A STUDY ON THE INCIDENCE OF MICROALBUMINURIA IN NON-DIABETIC NORMOTENSIVE SMOKERS

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CERTIFICATE

This is to certify that the dissertation entitled "**A STUDY ON THE INCIDENCE OF MICROALBUMINURIA IN NON-DIABETIC NORMOTENSIVE SMOKERS"** is the bonafide work of **Dr.P.RUDRESHWAR** in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in **April 2015**.

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DECLARATION

I **Dr.P.RUDRESHWAR.,** solemnly declare that, this dissertation "**A STUDY ON THE INCIDENCE OF MICROALBUMINURIA IN NON-DIABETIC NORMOTENSIVE SMOKERS** is a bonafide record of work done by me at the Department of General Medicine, Govt. Rajaji Hospital, Madurai, under the guidance of **Dr. R. BALAJINATHAN, M.D.,** Professor, Department of General Medicine, Madurai Medical College, Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of **M.D Degree General Medicine Branch-I;** examination to be held in **April 2015.**

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CONTENTS

ABSTRACT

Smoking is associated with an increased morbidity and mortality from various diseases of the body. It predisposes to chronic bronchitis, emphysema, cerebrovascular accident, tumours of the lung, gastrointestinal system, urinary tract, pancreas, etc. Microalbuminuria has been shown by many studies as a strong independent risk factor for cardiovascular disease. It also predicts the future risk of renal failure and is a marker of endothelial injury. Various studies have shown that smoking causes a dose dependent increase in urine albumin excretion. The aim of this study is to study the proportion of non-diabetic normotensive smokers with increased urine albumin and albumin creatinine ratio in an analytical cross sectional study. Our study population comprised of 120 non-diabetic normotensive and non-obese subjects taken from the general medicine outpatient clinic of government rajaji hospital. Relevant history and clinical examination was done. Smoker was defined as the one who had a smoking history of five or more pack years. Out of 120 patients 76 were smokers and 44 were non-smokers. The 44 non-smokers were age matched and taken as control. Fasting blood sugar, urea, lipids and one time screening of urinary albumin and urinary creatinine was done to exclude other comorbidities. In our study we found that smokers had significantly

higher levels of urine albumin and albumin creatinine ratio when compared to non-smokers. 69(90.8%) smokers and 7(15.9%) non-smokers had microalbuminuria. 63(82.9%) of smokers and 2(4.5%) of non-smokers had high urinary albumin creatinine ratio(ACR). The mean urinary albumin in smokers was 47.32mg/L and in non-smokers was 18.94mg/L. The mean urinary albumin creatinine ratio in smokers was 74.06micro g /mg and in non-smokers was 20.65micro g /mg. Microalbuminuria and urine albumin creainine ratio(ACR) were directly related to the amount of smoking in pack years. The high density lipoprotein was significantly reduced in smokers when compared to non-smokers(mean HDL in smokers 36.66mg/dl). The two groups were comparable in all other parameters.

KEYWORDS

MICROALBUMINURIA, SMOKING, URINE ALBUMIN CREATININE RATIO (ACR), PACK YEARS, HIGH DENSITY LIPOPROTEIN, END STAGE RENAL DISEASE.

INTRODUCTION

Smoking damages the vascular and various hormonal systems of the human body. It also plays a major role in thrombus formation, atheroma formation and occlusion of vessels. The smoke that emerges from a burnt tobacco contains not only nicotine but also more than 4000 chemical compounds as a result of pyrolysis and pyrosynthesis of tobacco. The smoke contains an aerosol part and a vapour part. The aerosol part gets deposited in the airways and also in the alveoli of the lungs.

Smokers are at a high risk of developing large vessel and small vessel atherosclerosis when compared to non-smokers. smokers are also at a high risk of developing carcinoma of the larynx, stomach, esophagus, pancreas, urinary bladder, ureter, kidney, cervix and other important organs. They are also at a high risk of developing haematological malignancies such as myeloid leukemia. Smoking also prolongs wound healing and causes several complications during pregnancy like placental abruption, placenta previa, etc. In women it also leads to early menopause. Skin wrinkling, cholelithiasis, impotence and adverse cardiovascular events are also caused by smoking. Smoking cessation leads to a reduced risk of occurrence of a second cardiovascular event and after 15 years of smoking the risk of developing an adverse cardiovascular event is almost the same as non-smokers.

Microalbuminuria is defined as urinary albumin excretion levels ranging from 30 to 300mg/24 hours. Overt albuminuria or macroalbuminuria is urinary albumin levels more than 300mg/24hours. Several studies in the past have focussed on microalbuminuria as a predictor of cardiovascular mortality. It predicts the future development of mortality, doubling of serum creatinine and end stage renal disease. Studies have shown that prevalence of microalbuminuria is almost double in smokers when compared to non-smokers. In diabetic population the smokers have a high risk of developing microalbuminuria and progression to proteinuria when compared to non-smokers. smoking has four important effects on the albumin excretion in diabetics,

1) Risk of developing microalbuminuria is increased.
2) Time period between onset of microalbuminuria and the diabetes is reduced.
3) Increases the rate of progression to persistent proteinuria
4) Increases the rate of progression to end stage renal failure
5) Increases the risk of development of ischemic nephropathy.

Our study is to aimed at finding put the proportion of non diabetic normotensive smokers having microalbuminuria when compared to non smokers and also the effect of smoking on urine albumin creatinine ratio.

AIM OF THE STUDY

→To study the proportion of non-diabetic normotensive smokers having micro-albuminuria and increased urinary albumin-creatinine ratio (ACR) in an analytical cross sectional study.

REVIEW OF LITERATURE

Tobacco smoke is a complex mixture consisting of over 5000 chemical compounds. These various compounds affect almost all systems of the human body. WHO estimates about 5.4 million premature deaths are due to smoking world wide. The most common causes of death due to smoking are cardiovascular disease, lung cancer and chronic obstructive pulmonary disease.

Here are some of the components and their harmful effects on the body,

1,3 butadiene	Reproduction.
Acetaldehyde.	Nasal olfactory epithelial lesions.
Acetone.	Nervous system.
Acrylonitrile.	Respiratory system.
Ammonia.	Respiratory system.
Carbon monoxide.	Central nervous system.
Chloroform.	Liver damage.
Copper.	Lung and immune system.
Ethyl benzene.	Liver and kidney.
Hydrogen cyanide.	Thyroid and nervous system.
Mercury	Nervous system.

Nickel.	Lung fibrosis.
Methyl chloride.	Cerebellum.
Phenol.	Lung, kidney, liver, CVS.
Toluene.	Colour vision, nervous system.
Tri ethyl amine.	Liver, kidney, nervous system.
Selenium.	Respiratory system.
Cresol.	Neurotoxicity.
Xylene.	Respiratory and nervous system.
Cresol.	Neurotoxicity.
Nicotine.	Cardiovascular, renal, lungs, etc.
2-nitropropane.	Liver.
Acetonitrile.	Multisystem.
Acrolein.	Nasal lesions
Acrylic acid.	Respiratory system.
Aniline.	Immune-related.
Benzene.	Decreased lymphocyte count
Chromium	Lower respiratory tract.
Cobalt.	Lung and immune system.
Diethyl formamide	Digestive system
Hexane.	Nervous system.

Formaldehyde.	Nasal irritation.
Hydrazine.	Liver.
Isopropyl benzene.	Kidney, adrenals.
Lead.	Nervous sytem
Manganese.	Neurobehavioral.
Methyl ethyl ketone	Nasal effects.
Nickel.	Lung fibrosis.
Propionaldehyde.	Atrophy of olfactory epithelium.
Pyridine.	Odour threshold.
Styrene	Nervous system.
Vinyl acetate	Nasal lesions
Propyl benzene	Increased organ weight

The TTC (threshold of toxicological concern) is a human exposure threshold below which there would be no appreciable risk to human health, despite the absence of chemical-specific toxicity data. It is usually a cut-off value based on experimental data. The FDA human TTC for oral exposure is 1.5 micrograms/day.

Smoking (cigarettes and beedis) is the third top risk for health loss in India, leading to nearly one million deaths every year. Between 1980

and 2012, smoking among Indian men decreased from 33.8 per cent to 23 per cent.

OXIDATIVE STRESS IN SMOKERS:-

The oxidative stress produced by smoking can be registered directly by measurement of reactive oxygen species production in peripheral blood or by the effects of oxidative stress on lipid peroxidation products and oxidized proteins or as the responses to the oxidative stress[(1)].

Effects of this oxidative stress on a variety of vital target molecules are more important than the presence of oxidative stress. There are many markers for oxidative damage including oxidation and nitration of proteins[(1)]. Proteins contain tyrosine residues and the nitration of these tyrosine residues leads to production of 3-nitrotyrosine which is a marker of nitric oxide dependent oxidative damage. Nitric oxide and peroxynitrite mediated formation of 3-nitrotyrosine is elevated in platelets and plasma of chronic smokers. Studies have shown higher levels of nitrated and oxidized fibrinogen, transferrin, plasminogen and ceruloplasmin in smokers[(1)].

Peroxidation of polyunsaturated fatty acids of cell membranes that amplify oxidative stress is caused by free radicals from cigarette smoke.

The F2-isoprostanes are produced from free radical catalysed lipid peroxidation of arachidonic acid. Smokers also contain increased level of isoprostane 8-iso-prostagalndin F2 (PGF2). Excretion of urinary 8-epi-PGF2 excretion was significantly increased in long term current and former smokers[(1)]. A does response relationship is present between the number of cigarettes smoked and both urinary cotinine and urinary 8-epi-PGF2 alpha. F2 isoprostane levels and 8-iso-PGF2 alpha are significantly increased in atherosclerotic plaques as well and this strengthens the hypothesis[(1)].

Increased levels of malondialdehyde which is a degradation product of lipid peroxides have been associated with current smoking status. Higher levels of thiobarbituric acid reactive substances(TBARS) have been found in smokers compared to non smokers. Studies have shown inverse association of percentage of predicted FEV1 and percentage of predicted FVC with TBARS in men and not in women suggesting gender differences in the relation of oxidative stress to pulmonary function[(1)].

Endogenous levels of antioxidants in the systemic compartment are depleted by the exposure to oxidant chemicals in the smoke. Thus smoking results in low antioxidant levels in the plasma. Trolox-equivalent antioxidant capacity (TEAC) is significantly lower in smokers compared to non-smokers.[(1)]

However studies have found no relationship between plasma levels of TEAC and spirometric end points (FEV1 or FEV1/FVC).

Lower serum levels of vitamin-c, alpha carotene, beta-carotene, beta-crytoxanthin, melatonin, alpha-tocopherol, and lutein/zeaxanthin have been found in smokers by the THIRD NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY and other studies. In addition an inverse relationship between plasma levels of vitamin C and beta-carotene corrected for habitual dietary intake and cigarette smoking has been found[(1)]. Such reduction in plasma antioxidants disturbs the normal oxidative-antioxidative balance in smokers.

Glutathione is a major antioxidant used to maintain vitamins C and E in their functional and reduced forms and to eliminate peroxides to nontoxic hydroxyl fatty acids[(1)]. The GSH is oxidised to disulphide form by the reactive oxygen species present in cigarette smoke resulting in decreased GSH levels.

Similar mechanisms result in an even more extensive oxidation of the cysteine /oxidised cysteine redox couple and reduced cys levels showing that smoking has additional effects on sulphur amino acid metabolism[(1)]. Since cysteine is a critical molecule for normal GSH

synthesis, the evaluation of the Cys/CySS redox couple may be a new sensitive maker of oxidative stress in smokers[1].

Elevated levels of peroxides and decreased traditional plasma antioxidants characterise the oxidative burden in the systemic compartment of smokers.

SYSTEMIC INFLAMMATION IN SMOKERS:

Systemic inflammation is characterised by an increase in circulatory mediators and activation and release of inflammatory cells in to the circulation[1].

INFLAMMATORY CELLS IN CIRCULATION

As a result of systemic inflammation the hematopoietic system gets stimulated resulting in the release of leukocytes and platelets in to the circulation. Long term cigarette smoking increases total WBC counts mainly polymorphonuclear cell counts in the blood. There is a does response relationship between WBC counts and pack years smoked.

Other associated changes that occur are the increase in number of circulating band cells (a hallmark of early marrow release of neutrophils) and increased expression of L-selectin on maturing polymorphonuclear cells[1]. L-selectin is important for the recruitment of

polymorphonuclear cells to the inflamed tissue as it initiates the adherence of PMNs to the endothelium[1].

PMNs from smokers contain higher level of myeloperoxidase enzyme. Circulating cytokines such as interleukin-1beta and interleukin-6 may be responsible for the bone marrow stimulation induced by lung inflammation[1]. These cytokines can also stimulate the marrow to release increased numbers of platelets.

T-lymphocyte counts are increased in humans exposed to smoke. CD4+ cells, CD8+ cells and CD4/CD8 ratio are increased in heavy smokers. Peripheral blood memory T cells and naïve T cells are increased in smokers compared to non-smokers[1].

INFLAMMATORY MARKERS IN PERIPHERAL BLOOD

Smoking activates inflammatory cells which produce a great variety of inflammatory mediators such as acute phase reactants and cytokines. Other conditions which produce an increase in cytokine levels include infection, trauma, tissue infarction, cancer, etc. These inflammatory mediators are potential markers of persistent and systemic systemic alterations.

These inflammatory mediators are raised in almost all parts of the body and are not just confined to the lung[1]. There is a strong independent

dose-response relationship between elevated levels of different acute phase reactants such as C-reactive protein, fibrinogen and smoking. Several studies support the hypothesis that CRP and fibrinogen levels in particular are related to pack years of smoking rather than to years since quitting smoking[(1)].

Studies have shown that CRP levels remain significantly elevated even 10 years after smoking cessation. Smoking cessation results in a rapid reduction in hemostatic and inflammatory markers, but CRP levels remain significantly elevated even after 10 to 19 years and do not revert to that of non-smoker levels until after 20 years[(1)]. CRP reduction is based on the number of cigarettes smoked.

Dose response relationship exists between the number of cigarettes smoked per day and plasma fibrinogen levels. Reduced lung function per se is associated with increased levels of C-reactive protein, blood leukocytes and fibrinogen[(1)]. So having both the risk factors (smoking and reduced lung function) suggests an additive effect contributing to higher levels of systemic inflammation in prone individuals.

Low FVC is associated with higher plasma levels of haptoglobin, ceruloplasmin, alpha1 acid glycoprotein, and higher levels of myocardial infarction and cardiovascular death.

Large prospective studies have shown increased levels of alpha1 antitrypsin, haptoglobin, fibrinogen, ceruplasmin, and alpha1 acid glycoprotein in healthy adult men with increasing cigarette consumption independent of other known cardiovascular risk factors[(1)]. It is also possible that high acute phase reactant levels in smokers may have a direct on the promotion of cardiovascular diseases.

Increased levels of CRP and fibrinogen have been associated with risk for cardiovascular events. CRP might not only be a biomarker but can have direct effects on the pathogenesis of endothelial dysfunction and atherosclerosis[(1)]. CRP stimulates endothelin-1 and interleukin-6 production and upregulates adhesion molecules and sets in motion a cascade of events that can lead to clot formation. It has also been shown to promote atherosclerosis in lipoprotein-E deficient mice.

Fibrinogen can promote cardiovascular disease through it effects on blood viscosity, fibrin formation and platelet aggregation. Thus CRP and fibrinogen levels are markedly increased in smokers possibly contributing to pro atherogenic and pro inflammatory effects of chronic smoking.

Raised acute phase reactant levels partially reflect elevations in inflammatory cytokines such as interleukin-6 and tumor necrosis factor[(1)]. Similar to acute phase reactants increased levels of pro inflammatory

cytokines like interleukin-6 and tumor necrosis factor alpha have been shown to be risk factor and predictor for myocardial infarction, stroke and coronary heart disease. Several studies have demonstrated raised levels of interleukin-6 and tumor necrosis factor levels in smokers[(1)].

Studies have shown that interleukin-6 levels were substantially increased in current smokers when compared to non smokers. A significant association was found between interleukin-6 and WBC counts, and interleukin-6 and fibrinogen emphasising the role of interleukin-6 as an inducer of fibrinogen

EFFECTS OF SMOKING ON MARKERS OF HEMOSTASIS, COAGULATION AND ENDOTHELIAL DYSFUNCTION:

There is a complex relationship between smoking and atherogenesis which leads to cardiovascular disease. Besides inflammation, vascular endothelial dysfunction, systemic hemostatic and coagulation disturbances, lipid abnormalities are some other mechanisms by which smoking increases the risk of cardiovascular pathology. Fibrinogen, tissue plasminogen activator antigen, fibrin d-dimer have been identified as predictors of subsequent cardiovascular events[(1)].

Platelet hyper aggregation, activation, plasma viscosity, and plasminogen activator inhibitor levels have been associated with cardiovascular morbidity and mortality[1].

Diminished production or availability of nitric oxide causes endothelial dysfunction. Smokers have significantly decreased serum concentration of nitrate, nitrite, metabolic end products of nitric oxide. LDL-low density lipoprotein is more prone to oxidation due to higher level of reactive oxygen species[1].

Oxidised LDL reduces the bioactivity of nitric oxide and this reduced bioactivity is strongly associated with increased inflammatory cell entry in to the arterial wall. Oxidised LDL is taken up by the macrophage scavenger receptors leading to foam cell formation and cholesterol ester accumulation.

Increased platelet/monocyte aggregation and upregulation of CD40/CD40L have been proposed as potential contributors to the atheroembolic complications of smoking[1]. CD40-CD40L ligand couple, members of TNF family are expressed by most cells involved in atherosclerosis. Smokers have elevated surface expression of CD40 on monocytes along with increased CD40L expression on platelet surface. Plasma cotinine concentrations correlate with rate of platelet-monocyte

aggregations and CD40 and CD40 ligand expressions. A recent study has shown the trigger for CD40/CD40L expression in human endothelial and smooth muscle cells to be oxidised LDL.[1]

Dysfunctional endothelial cells lose their property of non-adherence to immune effector cells. Smokers have shown to contain higher levels of P-selectin, E-selectin and soluble intra cellular adhesion molecule (ICAM-1) compared to non smokers. Dose dependent relationship exists between daily cigarette consumption, plasma cotinine levels, exhaled carbon monoxide levels and plasma ICAM-1 concentration[1].

HEMOSTASIS AND COAGULATION MARKERS:

Whole blood viscosity and its determinants: haematocrit and plasma viscosity, principally composed by plasma fibrinogen and lipoproteins are associated with subsequent cardiovascular events. Current smokers have increased plasma viscosity and/or haematocrit which results in a procoagulant state. Increased fibrinogen levels may be the cause of increased plasma viscosity seen in smokers[1].

Tissue plasminogen activator (t-PA) which is the main fibrinolytic activator that converts plasminogen to plasmin is synthesised from endothelial cells[1]. Due to the endothelial dysfunction that occurs in

smokers there is a major impairment of release of t-PA release from these cells.

The primary inhibitor of fibrinolysis, PAI-I inhibits plasminogen activation by binding with t-PA. smoking results in significant increase in t-PA antigen which represents PAI-I/t-PA complexes. This indicates impaired fibrinolytic activity smokers[(1)]. PAI-I levels are significantly higher in smokers and correlates with pack years of smoking.

Plasmin is responsible for maintain vascular patency by promoting degradation of fibrin thrombus and disintegrating clots. Fibrin d-dimer levels which are cross liked products of fibrin is related to cardio vascular risk[(1)]. Increased D-dimer levels are found in smokers which reflects increased coagulation activation because this antigen is produced from several degradation products from cleavage of cross-linked fibrin by plasmin.

Smoking is one of the important major life style factor influencing levels of a number of novel inflammatory, coagulation and hemostatic markers linked to common wide spread diseases in population-based prospective studies[(1)].

Endothelial dysfunction, low grade inflammation and systemic oxidative stress caused by smoking is one of the real working

mechanisms that explains increased prevalence of common diseases like coronary heart disease, peripheral vascular disease, and chronic obstructive pulmonary disease[1].

Genetic susceptibility also plays a role in smokers developing in these diseases. Linkage analysis of extended pedigrees and affected sibling pairs, Whole genome association studies and case control are used to dissect genetic components of complex traits.

Disease initiation and progression of the same is based on multiple genes interacting with many environmental factors where smoking is only one of the variables[1].

SMOKING AND CARCINOGENESIS:

Cigarette smoking causes over 1 million deaths related to cancer per year in the world and about 30% of all cancer deaths in developing nations. Lung cancer is the predominant malignancy caused by smoking. At the beginning of 20th century lung cancer was rare, but the incidence and mortality rate increased progressively as smoking became more popular[9].

The relationship between researched cigarette smoking and cancer is probably the most researched topic in the history of cancer epidemiology. The strongest determinant of lung cancer in smokers is duration of smoking, and as the number of cigarettes smoked increases so does the risk[9]. Smoking increases the risk of all types of lung cancer such as small cell carcinoma, squamous cell carcinoma, adenocarcinoma (including bronchiolar-alveolar carcinoma) and large cell carcinoma.

In the united states adenocarcinoma has replaced squamous cell type of cancer as the most common type of cancer caused by smoking. In india however squamous cell carcinoma remains as the most common type of lung cancer[9].

History of smoking was found in 87% of the males and 85% of the females with lung cancer.

Following are the percentage of tobacco related products smoked in india:-

1) Bidi- 28.4% to 79%
2) Cigarettes- 9.0% to 53.7%
3) Mixed-7.5 to 13.6%

Relative risk of developing lung cancer is 2.23 for cigarette smokers and 2.64 for bidi smokers with 2.45 as the overall RR. Bidi is

more carcinogenic when compared to cigarettes and this has been shown by studies by jussawalla & jain (1979) and pakhala. Hooka smoking has also been shown to be associated with lung cancer[9].

A recent study has shown smoking of bidi, cigarettes and hookah had similar ORs for cumulative consumption

Environmental tobacco exposure is a well known carcinogen associated with lung cancer. According to a meta analysis of 40 studies environmental tobacco exposure carries a relative risk of developing cancer of 1.48 (1.13-1.92) in males and 1.2 in females(1.12-1.29)[9]. with more exposure comes more relative risk. Work place exposure to environmental tobacco results in a relative risk of 1.16.

Childhood exposure to enviromnetal tobacco carries a OR of 3.9. there is increasing risk with increasing number of smokers and duration of exposure. Rapiti et al has also shown that childhood exposure to environmental tobacco is associated with the risk of developing lung cancer[9]. Odds ratio for women was 5.1 in that study. Asbestos, nickel, arsenic, radiation, haematie hard rock mining, chromium, chloromethyl, ester and mustard gas, soot and tar exposure are some other risk factors for lung carcinoma and smoking combined with these risk factors increases the risk greatly.

Cessation of smoking avoids the further increase in risk of carcinoma regardless of age. Risk of ex-smokers remains high for many years even after the cessation of smoking compared to the risk of never smokers[9].

Cigarette smoking is also a major risk factor of transitional cell carcinomas of ureter, bladder and renal pelvis. Similar to lung cancer the risk increases with the number of cigarettes and the duration of smoking and cessation avoids any further raise in the risk. Smoking is also associated with renal cell carcinoma[9]. Smoking is also associated with carcinomas of the oral cavity including the tongue and lip in both men and women. Smoking combined with alcoholism further increases the risk of oral cavity carcinomas.

Cigarette is smoking is also the risk factor of nasopharyngeal and sinonasal cancer. It is risk factor for hypopharyngeal carcinoma and the duration and number of cigarettes smoked increases the risk as in other carcinomas. Cigarette smoking also causes squamous cell carcinoma of the esophagus and adenocarcinoma of thr esophagus which has been increasing. The risk increases with increasing duration of smoking and risk remains elevated even after smoking cessation[9].

Laryngeal carcinoma is also caused by cigarette smoking and the risk increases with duration of smoking and the number of cigarettes smoked. Risk is greatly enhanced by alcohol consumption and decreases upon stopping smoking. Cigarette smoking is also a cause of liver cancer independent of hepatitis B, hepatitis C and alcoholism. Most studies show a relationship to cessation and dose. Smoking is also a cause of squamous cell carcinoma of the cervix[(9)].

Cigarette smoking is also related to myeloid leukemia. Carcinomas of hypopharynx, larynx, esophagus, oral cavity, oropharynx are strongly associated with cigar and/or pipe smoking. Does response relationship has been established by studies. Pipe/cigar smoking is also related to pancreas, urinary bladder and stomach carcinomas[(9)].

Carcinogens in smoke:-

A carcinogen is any agent that causes cancer or increases the incidence of cancer. The range of total exposure to carcinogens in smokers is approximately 1.4-2.2mg/cigarette. Strongest carcinogens such as polycyclic aromatic hydrocarbons, N-nitrosamines and aromatic amines occur in the lowest amounts while weaker carcinogens such as acetaldehyde, isoprene,etc occur in higher amounts[(9)].

PAH were first identified as carcinogenic constituents of coal tar and they are incomplete combustion products. They occur as mixtures in broiled foods, soots, tars, automobile engine exhaust, and other material created by incomplete combustion. PAH are usually locally acting carcinogens, for example benzopyrene has powerful local carcinogenic activity[(9)]. Mouse skin has been used to evaluate the carcinogenicity of PAH. PAH also causes cancer of lung, mammary glands, trachea depending on the route of administration.

Nitrogen containing analogues of PAH and compounds such as furan are heterocyclic compounds. Furan is a liver carcinogen. N-nitrosamines are another huge class of carcinogenic agents which has demonstrated activity in over 30 different animal species. They are potent systemic carcinogens that affect various tissues. N-nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N-nitrosonornicotine (NNN) are tobacco specific nitrosamines found only in tobacco products[(9)].

NNK causes lung tumors in many almost all animal species on which it is tested on and has particularly high activity in rat. NNN can also induce tumors of liver, nasal cavity, and pancreas[(9)]. NNN also predisposes to respiratory tract tumors, nasal tumors, and esophageal

tumors. NNN and NNK have been shown to induce all these tumors in humans[9].

2-naphthyl amine and 4-aminobiphenyl are aromatic amines first classified as human carcinogens due to exposures to due in industries. They both are combustion products and all well known to cause human bladder carcinoma[9]. Broiled foods contain heterocyclic aromatic amines which as also combustion products found in cigarette smoke.

Aldehydes such as acetaldehyde and formaldehyde are also potent carcinogens found in tobacco smoke. They are also endogenous metabolite in human blood. Phenolic compounds such as caffeic acid and catechol also harbour carcinogenic potential. Glandular tumors of the stomach can be caused by relatively high doses of catechol. 1,3-butadiene and benzene are two very strong carcinogens present I cigarette and they are both multi-organ carcinogens[9].

Vinyl chloride and ethylene oxide are other important carcinogens found in smoke in substantial quantities. Malignancies of the lymphatic and hematopoietic system are cause by ethylene oxide. Diverse metals are also found in smoke. cigarette smoke contains substantial amount of free radicals. Quinone-hydroquinone is a major free radical complex[9]. Studies have shown that cigarette smoke consists of an uncharacterised

ethylating agent with ethylated haemoglobin and DNA paving the way for carcinogenesis. Although there are various well characterised carcinogens in cigarette smoke PAH, benzene, ethylene oxide, aldehydes and aromatic amines are the most important due to their high carcinogenic potency[9].

Table- carcinogens and tobacco induced cancers

CANCER TYPE	LIKELY CARCINOGEN
1) Lung	PAH, NNK, aldehydes, 1,3-butadiene, isoprene, ethyl carbamate, benzene, ethylene oxide
2) Larynx	PAH.
3) Nasal	NNK, NNN, aldehydes and other nitrosamines.
4) Esophagus	NNN, other N-nitrosoamines.
5) Liver	NNN, other nitrosamines, furan
6) Pancreas	NNAL, NNK
7) Leukemia	Benzene
8) Cervix	NNK, PAH
9) Bladder	4-aminobiphenyl

MECHANISMS OF TUMOR INDUCTION BY CIGARETTE SMOKE:-

The major established pathway of cancer causation by cigarette smoking involves exposure to carcinogens, the formation of covalent bonds, formation of DNA adducts and the resulting mutations in critical genes of somatic cells[9]. Somatic mutations do not affect their descendants since somatic mutations occur only in somatic cells. The somatic mutation theory of cancer is well established and the presence various different type of carcinogens in cigarette smoke is consistent with the theory.

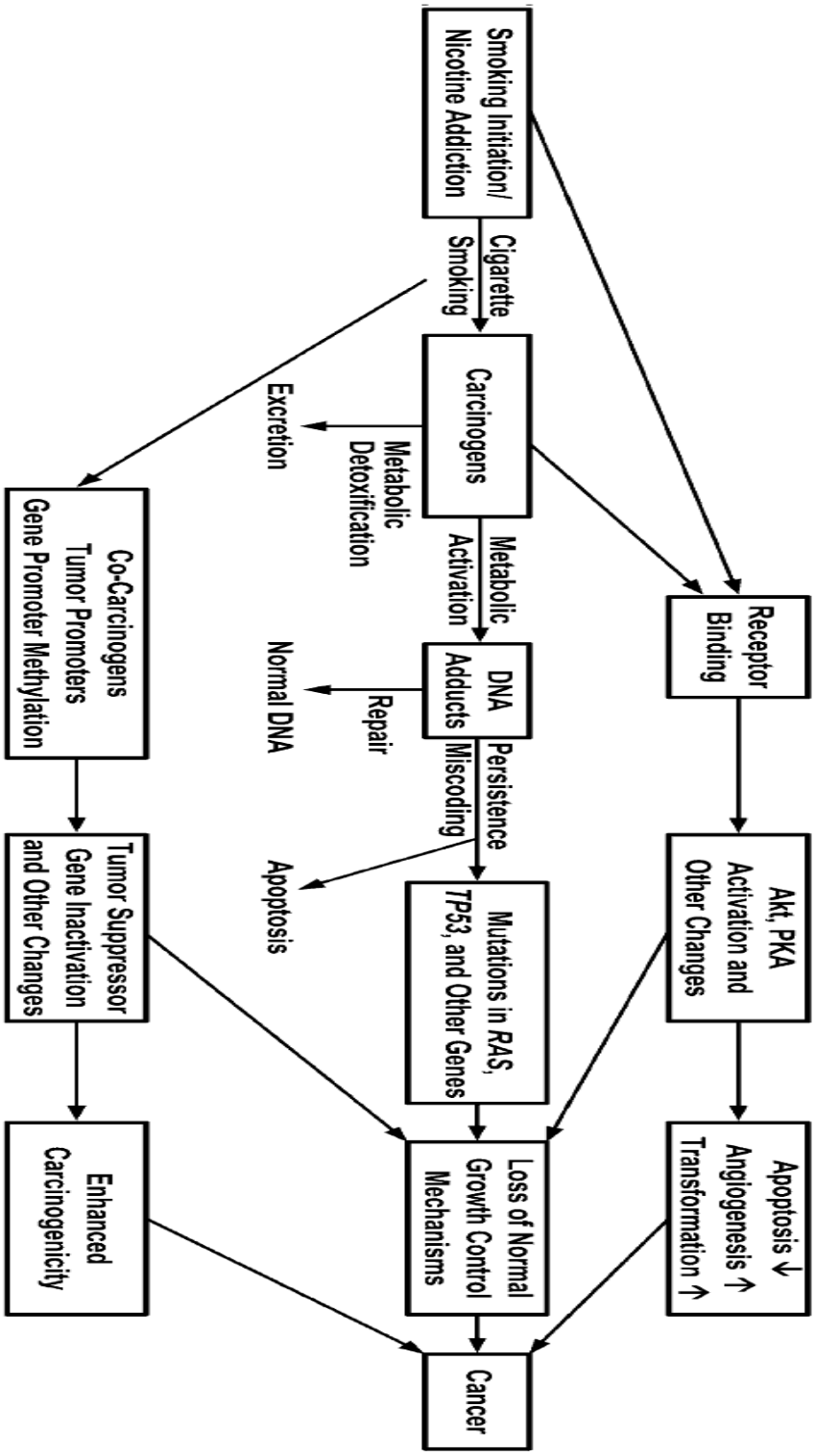
People usually start smoking as teenagers generally due to peer pressure[9]. Some get addicted to nicotine and some smoke habitually. However nicotine is not the carcinogenic component of smoke. Each puff of cigarette contains a mixture of various different type of carcinogens along with thousands of other type of compounds.

Most of cigarette smoke carcinogens require to be activated before they can function as carcinogens and this activation is metabolic and generally catalysed by cytochrome P450 enzymes which convert them to electrophilic entities. These electrophilic compounds covalently bind to DNA , forming DNA adducts[9].

P450s such as 1A1 and 1b1 are induced by cigarette smoke via interactions with receptors of aryl hydrocarbon. These p450s play a crucial role in the metabolic activation of PAH. The inducibility of these enzymes is a critical aspect of cancer susceptibility in smokers. P450s such as 2A13, 2E13, 1A2 and 3A4 also play a crucial role in the activation of carcinogens from cigarette smoke[(9)].

Metabolic detoxification is a process that results excretion of carcinogenic metabolites in harmless forms. This is catalysed by enzymes such as UDP-glucuronosyl transferases and glutathione-S-transferases. Metabolic detoxification and metabolic activation mechanisms compete with each other[(9)]. The balance between carcinogen detoxification and activation varies among individuals and those with lower detoxifying capacity are at a higher risk and those with a higher detoxifying capacity are a lower risk for developing cancer.

The formation of DNA adducts due to the metabolic activation of carcinogens are absolutely central to the carcinogenic process. various studies [have] demonstrated that DNA adduct levels in the lung and other tissues are higher in smokers than in non-smokers using relatively non-specific adduct measurement methods[(9)]. Some studies have shown that higher adduct levels are linked to higher probability of cancer.


Smoking Initiation/
Nicotine Addiction
Cigarette
Smoking
Carcinogens
Excretion
Metabolic
Detoxification
Metabolic
Activation
DNA
Adducts
Normal DNA
Repair
Persistence
Miscoding
Apoptosis
Receptor
Binding
Co-Carcinogens
Tumor Promoters
Gene Promoter Methylation
Tumor Suppressor
Gene Inactivation
and Other Changes
Enhanced
Carcinogenicity
Mutations in RAS,
TP53, and Other Genes
Akt, PKA
Activation and
Other Changes
Loss of Normal
Growth Control
Mechanisms
Apoptosis ↓
Angiogenesis ↑
Transformation ↑
Cancer

When adduct levels increase in the body cellular repair mechanisms remove them and return the DNA structure back to normal. Various repair mechanisms exist such as excision of DNA damage by base, nucleotide excision repair, mismatch repair, direct base repair by alkyltranferases and double strand repair[9]. If these enzymes are damaged for example due to DNA damage or for other reasons they are unable to carry out their function then the adducts will persist, accumulate leading to a high risk of cancer. There are also polymorphisms in some DNA repair enzymes that lead to a deficient repair enzyme leading on to a high risk of cancer development.

Persistent DNA adducts lead to miscoding during DNA replication when incorrect processing by DNA polymerases occur. There is a high specificity in the relation between the types of mutation and the DNA adducts produced by cigarette smoking. G to A and G to T mutations are frequently observed[9].

In cigarette smoke induced cancers mutations in the KRAS oncogene in lung cancer and TP53 tumor suppressor gene are frequently observed. Many studies have established the cancer causing role of these genes. In lung cancer the metabolically activated PAH causes damage to DNA leading on to mutations in TP53 and KRAS genes which predispose to lung cancer[9].

Cigarette smoking strongly linked with chromosomal damage damage throughout the airway tract and digestive tract and numerous mutations have been observed in lung cancer. Mutations lead to genomic instability, cellular proliferation and cancer due to loss of normal cellular growth control functions[9]. These mutations act through a complex process of signal transduction pathways. Programmed cell death or apoptosis is a process that removes cells with DNA damage ad serves as a counter measure to these mutational events. The balance between mechanisms supressing apoptosis and leading to it have a profound impact on tumor growth.

Epigenetic pathways also contribute to carcinogenesis. Nitrosamines and nicotine bind to nicotinic and cellular receptors resulting in the activation of protein kinase B (also known as Akt), protein kinase A and other changes[9]. And these changes result in increased angiogenesis, increased transformation and decreased apoptosis.

Cigarette smoke results in activation of cyclo-oxygenase-2 and epidermal growth factor. Tumor promoters and other co-carcinogens also occur in tumor smoke. In smokers promoter region on genes undergo enzymatic methylation resulting in gene silencing and this another important epigenetic pathway[9].

If gene silencing occurs in tumor suppressor genes it leads to unregulated proliferation.

SMOKING AND DYSLIPIDEMIA:-

Cigarette smokers are at increased risk for accelerated or premature peripheral, coronary and cerebral atherosclerotic vascular disease. They also at increased for myocardial infarction. The risk is one to three fold high in smokers[(7)]. Several possible explanations have been given by studies for these events. Some of these are increased arterial blood coagulation, damage to endothelium of arterial wall and changes in blood lipoprotein and lipid concentration.

Lipoprotein abnormalities are one of the major and essential risk factor for the occurrence of atherosclerotic vascular disease. Many studies have shown smokers have a rise in plasma total cholesterol, high low density lipoprotein (LDL), high very low density lipoprotein (VLDL), and high triglyceride levels. High density lipoprotein levels are decreased in smokers[(7)].

Many studies have established a definite correlation between lipid profile abnormalities and smoking. They have also established a dose response relationship between amount of cigarettes smoked, duration of smoking and changes in lipid profile[(7)].

Tobacco contains many compounds. Nicotine is one of the main compounds. Which can lead to an increase in VLDL, cholesterol and triglyceride levels. It also leads to a decrease in HDL levels. Nicotine increases the circulating pool of atherogenic LDL through increased transfer of lipids from HDL and reduced clearance of LDL from plasma compartment[7]. Thus this leads to increased deposition on LDL cholesterol in the arterial wall. High density lipoprotein has an inverse relationship to the risk of coronary heart disease. Lower the level of high density lipoprotein higher is the risk of coronary artery disease[7].

SMOKING AND DIABETES:-

Smoking increases sympathetic nerve activity, which increases vascular tone and energy expenditure. It also leads to secretion of corticosteroids leading on to increased burden on the heart. After decades of studies it has been revealed without that chronic smoking leads to high risk of developing insulin resistance and many aspects of insulin resistance syndromes leading on the development of type 2 diabetes mellitus. The risk is independent of nicotine induced vascular events and is highly related to degree of smoking[5].

It has been reported that heavy smokers had a 61% higher risk and those who smoked less than 20 cigarettes per day had a 29% increased risk.

Nicotine on insulin action:-

Studies have shown that smoking leads to disorders of glucose and lipid metabolism such as low HDL and hyperglycemia by reducing sensitivity. Cigarette smoking worsens glycemic control in a patient with diabetes mellitus. High doses of insulin are needed to achieve glycemic control in smokers when compared to non-smokers with diabetes[(5)].

Studies conducted in rats have shown that the offspring of nicotine treated rats possibly as a result of increase in body fat. The fasting blood glucose levels of these off springs were found to be higher than the fasting blood glucose of a different group of off springs. In addition the glucose levels at 30 and 120 minutes after an oral glucose load were significantly high in the offsprings of nicotine treated rats than in the offsprings of normal rats[(5)].

In another study conducted using nicotine infusion in healthy and diabetic volunteers, the insulin levels were not different between the two groups but insulin levels were required at higher quantities than before in diabetic volunteers. This shows that nicotine is more sensitive in type 2

diabetes patients in affecting the action of insulin on raised blood glucose. Young smokers also demonstrated reduced insulin mediated glycogen synthesis from the muscle[5].

These findings suggest that nicotine exposure both acute or chronic can impair insulin action in smokers not having diabetes and cause known diabetic patients to develop insulin resistance leading to higher requirement of insulin.

Nicotine on Beta cells of pancreatic islets:-

Many studies have shown found neuronal nicotinic acetyl cholinergic receptors expressed on many non-neuronal cells which include pancreatic islets[5]. An endogenous pancreatic mechanism modulates the action of basal insulin. Studies have shown that neuronal nicotinic acetyl cholinergic receptors use an intraganglionic mechanism to modulate insulin secretion. Another study has demonstrated that the mRNA for the subunits of neuronal nicotinic acetyl cholinergic receptors are expressed on insulin secreting cells using reverse transcriptase polymerase chain reaction. It has been shown that apart from long term exposure acute exposures can also cause a reduction in insulin secretion. These studies suggest that neuronly nicotinic acetyl cholinergic receptors play a vital role in insulin secretion[5].

Another study has shown that acute exposure to nicotine in levels higher than1 Mmol/L led to reduced high blood glucose mediated inslin release. It has further been shown that exposure to nicotine for more than 48 hours led to inhibition of insulin release even at basal blood glucose levels[5].

These studies prove that nicotinic receptors are present in pancreatic islet cells and these receptors play a role in affecting pancreatic beta cell function. The presence of these receptors serve as a switch to modulate insulin secretion physiology by cigarette smoking[5].

It has been shown by many studies conducted in various animals that apoptosis of pancreatic beta cells are increased by nicotine. In rats nicotine exposure in pre natal period led to impairment of endocrine part of the pancreas and it also led to increased adipose tissue development. These studies have demonstrated a direct link between fetal nicotine exposure and the development of metabolic syndrome. Another study has shown that nicotine mediated beta cell apoptosis, loss of beta cell mass, etc are carried out through the death receptor pathway of the mitochondria[5]. This apoptosis of beta cells caused by nicotine leads to development of postnatal glucose intolerance and increase in adipose tissue leading to obesity. Another study conducted by bruin et al has aslso demonstrated the apoptosis beta cells caused by nicotine. This study

suggests that high nicotine levels in smoking mothers act via the pancreatic neuronyl nicotinic acetyl cholinergic receptors and lead to oxidative stress in the islet cells and as a result of this oxidative stress that apoptosis of pancreatic islet beta cell occurs[5].

All studies have indicated that exposure to nicotine in pre or neonatal period leads to loss of beta cells of pancreas and thus leading on to reduced insulin secretion. Nicotine action on the neuronyl nicotinic acetyl cholinergic receptors lead to inflammation, oxidative stress and dysfunction on mitochondria. These findings suggest the possible mechanisms for the development of insulin resistance in diabetic patients who smoke and smokers developing glucose intolerance leading on to type 2 diabetes mellitus[5].

SMOKING AND INFECTION:-

Smokers are at increased risk of contracting bacterial infections. Smoking leads to increased risk of infections such as tuberculosis, pneumonia, legionnaires disease, chlamydial and gonococcal infections, helicobacter pylori infection, meningitis, nosocomial and post op infections[8].

Cigarette smoking can increase risk of infections in general by three different machanisms which include

1) Smoking induced structural and physiological changes.
2) Smoking related increase in bacterial virulence.
3) Smoking induced immune system deregulation.

All these mechanisms can occur one at a time or all three simultaneously [8]. For instance cigarette smoking play directly affect colonization of respiratory tract by bacteria which leads to reduced mucocliliary clearance and at the same time cigarette smoke induces bacterial components that play a role in binding of the bacteria to the respiratory epithelium and impairing the ability of the respiratory phagocytes to fight against the infection causing bacteria[8].

Smoking related structural changes and changes related to physiology occur predominantly in the respiratory tract and vascular endothelium. The effect of nicotine in blood vessels are different for different vascular beds. For instance cigarette smoking causes vasoconstriction in the peripheral arteries but it causes vasodilation in cerebral vessels. And in periodontal tissues it suppresses the angiogenesis of the related vessels and it is reversible in cessation if smoking[8].

These suggest that the increased bacterial infection in smoking in respiratory tract is due to reduced mucociliary clearance of the pathogens and in other systems is due to the reduced effectiveness of the immune system due to vasoconstriction and inhibition of angiogenesis[8].

Passive exposure of cigarette smoking in infants is a risk factor for sudden infant death syndrome. One of reasons for this is the influence of low levels of nicotine and cotinine on the toxins of pathogenic bacteria such as enterobacter and staphylococcus. It has also been shown that nicotine also exhibits lethal synergy with the toxins of pathogenic bacteria present in periodontal tissues. Such as fusobacterium. Some studies have also demonstrated that smoking is a risk factor for development of reservoir of chlamydia pneumonia in the epithelium of respiratory tract. Some studies have shown that cigarette smoking increases the growth of common bacteria present in the respiratory tract such as staphylococcus sanguis. While some other studies have shown that smoking has little effect on gram negative bacteria and inhibits the growth of gram positive organisms[8].

The same studies also report that due to this smokers have reduced high risk of developing severe gram negative bacterial colonization in the oral cavity. Smoking women are at an increased risk of developing bacterial infection. In these women the vaginal lactobacillus population decrease and anaerobic bacterial growth is facilitated due to the impaired phagocytosis as a result of smoking[8].

Cigarette smoking is capable of affecting neutrophil and monocyte function by both indirect and direct mechanisms. As a proof of this various innate cell receptor-tobacco agonist couples have been identified. The functions of phagocytic and antigen presenting cells have been compromised by the tobacco smoke. The generation of respiratory burst by neutrophils is reduced by smoking resulting defective killing of pathogenic bacteria. Cigarette smoke exposure suppresses the response of the innate immune system cells to lipopolysaccharide due to down regulation of receptors involved in bacterial killing such as TLR-2 and MARCO[8]. The innate immune system also develop impaired ability to produce free oxygen species needed for bacterial killing. Cigarette smoking also impairs the ability of dendritic cells to process antigen and their maturation is also suppressed[8]. This leads to reduced expression of co

stimulatory molecules such as MHC class II, CD80 and CD86 which as required for the antigen processing. The ability to produce T cell stimulatory cytokines is also reduced. Which are very important in curtailing gram negative bacterial infection [8].

In smokers IgG produced against bacteria are reduced and IgE levels are raised. B cells require cytokines that are released from T helper cells to proliferate, become plasma cells and produce immunoglobulins . It has been shown that smoker's exhibit reduced T cell proliferative responses.

ANATOMY OF THE KIDNEY:-

There are two kidneys and they are situated in the retroperitoneal region. They are placed on either side of the vertebral column. The lower pole of each kidney lies at the level of L3 and the upper pole of each kidney lies at the level of T12 vertebra. The weight of each kidney is about 125 to 175g in males and 115 to a55g in females. The length of each kidney is about 11 to 12 cms, width is about 5 to 7.5 cms and the thickness of each kidney is about 2.5 to 3cms[42]. The medial surface of each kidney contains the hilum through which the renal vein, artery , lymphatics, nerve plexuses pass in to the kidney. The fibrous capsule surrounding the kidney can be removed easily.

Renal artery enters in to the hilum of the kidney and divides in to two branches, the anterior and posterior respectively. Each anterior branch divides in to 3 lobar or segmental or lobar arteries and supplies the anterior of kidney. The posterior surface of the kidney is supplied by the posterior branch and it rarely gives rise to an apical segmental branch. There are no collaterals between the arterial branches.

Renal parenchyma consists of the renal cortex and renal medulla. 8 to 18 renal pyramids are present in the medulla. The cortico medullary junction houses the base of the pyramids and the apex is placed towards the renal pelvis and forms the papilla[(42)].

The collecting duct opens in to the papilla. The cortex is about 1cm in thickness and it covers the renal pyramid and it extends between the pyramids to form the renal columns of bertini. Longitudinal elements known as the medullary rays of ferrein extend in to the cortex. The medullary rays are composed of the proximal, distal tubules and collecting ducts and they form a part of the renal cortex.

The upper urinary tract is represented by the renal pelvis and it is lined by the transitional epithelium. Two or three major calyces extend from the renal pelvis[(42)]. Several minor calyces extend from the major calyces and extend toward the papillae and drain the urine. The length of the ureters

are around 28 to 34cms and they arise from lower part of the renalpelvis and open in to the bladder. The wall of the ureters are line by smooth muscle and this smooth muscle contracts sequentially to drain to the bladder.

THE NEPHRON:-

The functional unit of the kidney is the nephron and each kidney consists of about 4 lakh to 1.2 million nephrons[42]. The parts of the nephron consist of renal corpuscle, duct, loop of henle, distal tubule and proximal tubule.

The nephron arises from the metanephric blastema and the collecting ducts arise from the ureteric bud. The nephrons are divided in to 2 groups, they are the ones with a short loop of henle and the other group with a long loop of henle. Cortical nephrons have short loop of henle and those from medulla have along loop of henle. The loop of henle has an ascending and descending limb.

RENAL CORPUSCLE:-

The renal corpuscles contain capillaries lined by endothelial cells, mesangial cells with matrix, the parietal and visceral layer of Bowman's capsule with its basement membrane. The diameter of the glomerulus is about 200 Mm[42]. This diameter varies with location. The ultra filtrate of

the plasma is produced by the glomerulus. The filtration barrier consists of foot processes of visceral epithelial cells, basement membrane and endothelium.

The glomerular capillaries consist of many fenestrated endothelium, numerous intermediate filaments and microtubules are found in the endothelium[42]. The fenestrations are surrounded by the filaments. The reason for the negative charge in the endothelium is podocalyxin. Nitric oxide which is a vasodilator and endothelin-1 which is a vasoconstrictor are synthesised by endothelial cells. Vascular endothelial growth factor (VEGF) is synthesised by visceral epithelial cells and this increases permeability of endothelial cells by increasing the formation of fenestrations in the endothelium and this is essential for survival and rapair of endothelial cells in glomerular pathology.

The first barrier to prevent the passage of blood components from reaching the bowmans space are the endothelial cells.

VISCERAL EPITHELIAL CELLS:-

The distance between two podocyte foot processes is 25 to 60 nm[42]. This is called the filtration slit and it is covered by filtration slit membrane. The filtration slit diaphragm consists of a central filament. a main component of the filtration barrier is a protein called nephrin. It is the

product of the gene NPHS1. Mutation of NPHS1 gene is seen in congenital nephrotic syndrome or finnish type. This gene is located in chromosome 19. Nephrin protein is seen in the slit diaphragm. The nephrin is bound to cytoskeleton By CD2Ap. Congenital nephritic syndrome is associated with deletion of this CD2AP. Steroid resistant nephrotic syndrome is associated with mutation of a gene coding for the protein, podocin.

Podocalyxin is responsible for the negative charge seen in podcoytes. The visceral epithelial cells also contain the heymann nephritis antigen. The shape of the foot processes is maintained by podoplanin[42]. The visceral epithelial cells play a vital role in formation of the basement membrane.

MESANGIAL CELLS:-

The mesangial matrix and mesangial cells constitute the mesangium. The mesangial cells are irregularly shaped with elongated cytoplasmic processes and contain a dense nucleus. The cells contain many microfilaments like actin, actinin and myosin. These mesangial cells bridge the gap between capillaries and glomerular basement membrane and this prevents capillary distention.

The mesangial matrix is comprised of collagens and glycosaminoglycans. The mesangial cells contains properties of a smooth muscle cell and it

represents a specialised pericyte. These cells have contractile properties, produce mesasngial matrix and regulates GFR and also have phagocytic properties.

GLOMERULAR BASEMENT MEMBRANE:-

The basement membrane of the glomerulus consists of lamina densa which is a dense layer and two thinner layers the lamina rara interna and the lamina rara externa. The key component of the basement membrane is the collagen IV. The mutations in the genes coding for 3,4,5 collagen chains give rise to alports syndrome. The basement membrane has a negative charge. Heparin sulphate and other glycosaminoglycans make up the anionic sites in the basement membrane[(42)].

PARIETAL EPITHELIAL CELLS:-

These cells belong to the squamous type of epithelial cells. These cells give rise to crescents in rapidly progressive epithelial cells.

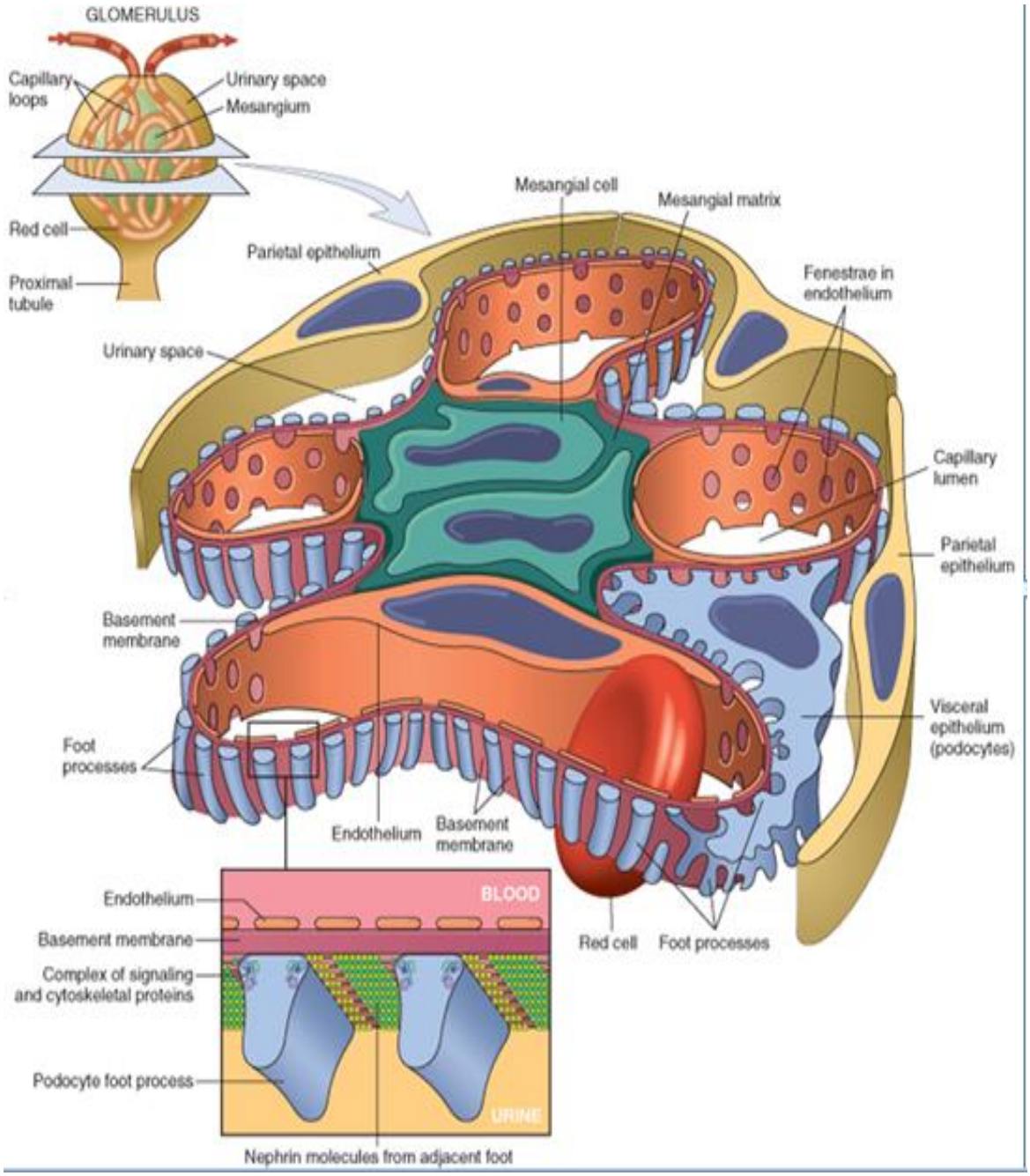


FIGURE SHOWING THE STRUCTURE OF A GLOMERULUS.

JUXTA GLOMERULAR APPARATUS:-

The juxta glomerular apparatus is a vital part of the kidnay and is located at the vascular pole of the glomerulus at the point where the glomerulus comes in contact with a part of the thick ascending limb. The vascular potion of the juxta glomerular apparatus consists of the afferent arteriole, the mesangial region and the efferent arteriole. The macula densa makes up the tubular part of the juxta glomerular apparatus.

JUXTAGLOMERULAR CELLS:-

These are the specialised cells that are seen in the walls of areterioles and the mesangial region[(42)]. These cells have smooth muscle cell and epithelial features. These cells contain granules containing renin and their precursors.

EXTRA GLOMERULAR MESANGIUM:-

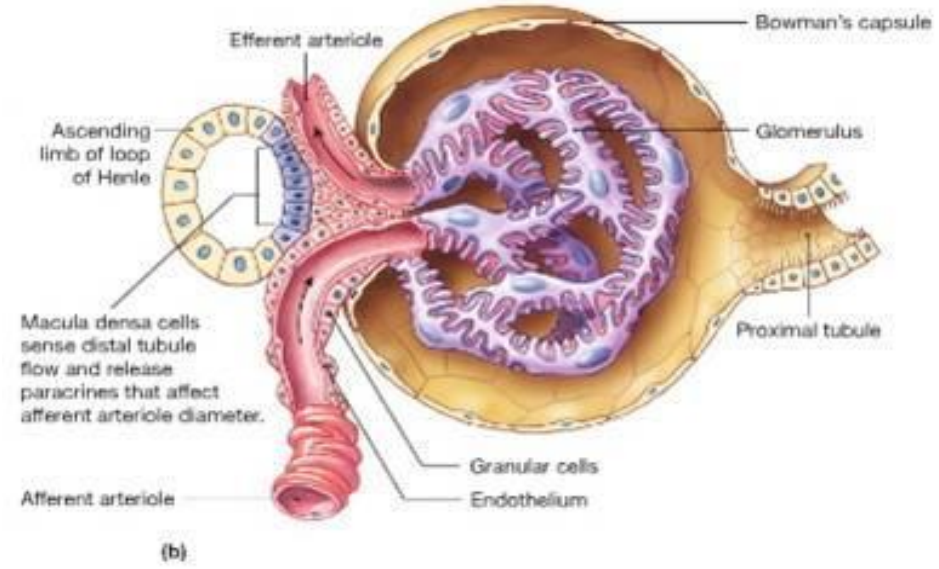
This part is also known as the LACIS or the cells of GOORMAGHTIGH. These are in contact with the macula densa and present in between afferent and efferent arterioles.

MACULA DENSA:-

This forms a part of the thick ascending limb. It consists of columnar cells and is a major part of renin- angiotensin system. It plays a major role in

regulating glomerular filtration rate, renin secretion and arteriolar resistance.

The changes in sodium concentrations in the tubules are sensed by this macula densa and the signal is transferred to the glomerular arterioles to control the GFR. The signal is also transferred to the renin secreting cells which are present in the afferent arteriole[42].



PROXIMAL TUBULE:-

It consists of a convoluted portion and a straight portion known as the pars recta and begins in the urinary pole.

LOOP OF HENLE:-

This functions as the counter current multiplier and plays a role in the concentration of urine.

DISTAL TUBULE AND COLLECTING DUCT:-

This plays a role in urine acidification and concentration.

ALBUMINURIA

Albuminuria is a well known predictor of poor renal outcomes in patients with type 2 diabetes mellitus and systemic hypertension. It has also been shown by many studies to be a predictor of cardiovscular outcomes in these in diabetic and hyeprtensive populations. Studies have shown that reducing albuminuria leads to reduced risk of cardiac and renal events[(11)].

Albuminuria is of five different types,

1) Microalbuminuria- 30 to 150 mg /24 hours
2) Mild- 150 to 500mg /24 hours
3) Moderate- 500 to 3000mg /24 hours
4) Heavy- 1000- 3000mg /24 hours
5) Nephrotic range- 3000- 3500 mg /24 hours.

METHODS FOR MEASURING URINE PROTEIN:-

DIPSTICK:-

This method uses the principle that says that presence of protein in a buffer solution causes a pH change which is proportional to the concentration of the protein itself. The dipstick contains a protein sensitive pH indicator dye and a buffer. The indicator changes colour which ranges from pale green to green and blue when the stick is moistened with urine containing the proteins. This test is more sensitive to albumin and very less sensitive to immunoglobulin light chains and globulins[10]. Therefore accurate quantification methods are necessary. Some of the examples of such methods are turbidimetry, dye binding techniques (ex- pyrogallol red-molybdate colorimetric method or benzthonium chloride method).

The dipstick results are interpreted as follows

1)negative- <15mg/L

2)1+ :30-100mg/L

3)2+: 100 – 300mg/L

4)3+: 300 – 1000mg/L

5)4+: >1000mg/L

Extremely alkaline urine produces a false postitve result.

Nowadays albumin specific dipsticks are available and these are very useful to detect low grade albuminuria. Some strips can also measure albumin:creatinine ratio[10].

Dipstick interpretation in albumin specific dipstick,

+ = 800mg/L

++ = 1450mg/L

+++ = 3000mg/L

TABLE SHOWING THE METHODS FOR MEASURING ALBUMINURIA:-

Table 1—*Measurement of albuminuria*

	Normal	Microalbuminuria	Macroalbuminuria	Advantages	Disadvantages
Dipstick for Protein	−	−	+	Convenience	Dependent on level of hydration
24-h protein (mg)	<150	<500	≥500	Overcomes problem of diurnal variation in excretion	Subject to collection errors
24-hour albumin (mg)	<30	30–300	>300	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Timed collection (μg/min)	<20	20–200	>200	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Spot collection (μg albumin/mg creatinine)	<30	30–300	>300	Convenience Not dependent on hydration level Most reproducible	Ratios vary based on sex

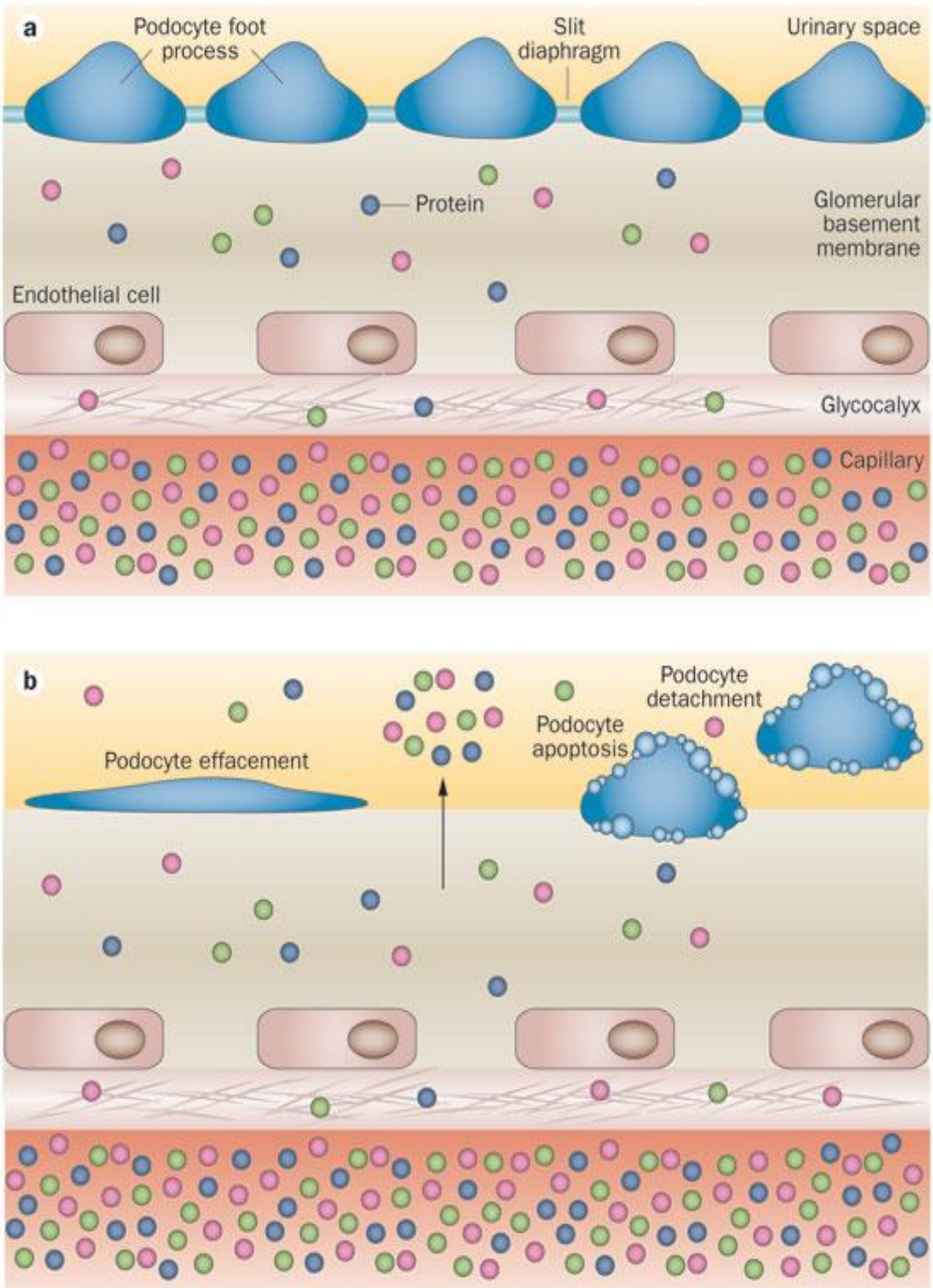


FIGURE SHOWING THE PODOCYTE FUNCTION

SULFOSALICYCLIC ACID METHOD:-

Sulfosalicylic acid precipitates proteins in the urine and the turbidity results as a result of this precipitation. This turbidity is proportional to the urine protein concentration. This method unlike the dipstick method detects albumin, globulins and immunglobulin light chains[10].

This test is rarely used nowadays due to enviromental safety concerns.

24 HOUR PROTEIN EXCRETION:-

This is the gold standard method. It gives the average of the variation of the protein excretion that occurs as a result of circadian rhythm and it is the most accurate method for monitoring proteinuria during treatment. The disadvantages with this method are as follows,

1) Error as a result of over or undercollection.
2) Error due to undercollection.

This method unlike dipstick quantifies total protein rather than just albumin and hence his results in the detection of light chains which is useful in diagnosing diseases like multple myeloma[10].

PROTEIN-CREATININE RATIO:-

This is an alternative method to 24 hour urine protein[10]. The advantages in this method are as follows,

1)not cumbresome

2)not affected by diuretics or variation in water intake.

3)the same sample can be used for microbial analysis.

A strong correlation exists between 24 hour urine protein and random urine sample protein creatinine ratio. An elevated protein creatinine ratio should always be quntified and confirmed with a 24 hour urine protein. A normal protein creatinine ratio rules out pathological proteinuria. This method is not very reliable for monitoring proteinuria during treatment.

SPECIFIC PROTEIN ASSAYS:-

Electrophoresis on cellulose acetate or agarose can be used for qualitative analysis of urine protein after concentration of the protein or by use of stains such as silver and gold which are very senstitive[10]. SDS-PAGE(sodium dodecyl sulfate-polycrylamide gel electrophoresis) identifies different proteins in the urine by molecular weight and it is also useful to find out the pattern of

proteinuria. Single protein measurement might also be beneficial. Neutrophil geltinase associated lipocalin can be used for very early detection of acute kidney injury.

Immunoglobin light excretion is suscpected if the dipstick protein is negative but the 24 hour urine protein is elevated. Immunofixation is used to confirm this[10].

Ratio of clearance of IgG to the clearance of transferrin can be used to assess the selectivity of proteinuria in nephrotic syndrome. The molecular weight of IgG is 160,000 and the molecular weight of 88,000. Highly selective proteinuria suggests the possiblity of minimal change disease. This also prevents responsiveness to corticosteroids. Selectivity of proteinuria along with low molecular weight protein excretion such as alpha-1microglobulin is reported to predict response to therapy and outcome in minimal change disease, membraneous nephropathy and focal segmental glomerulosclerosis[10].

MICROALBUMINURIA IN HYPERTENSION AND TYPE 2 DIABETES:-

In a study which involved 787 patients in the age group of 18-72 years it was found that discontinuation of the antihypertensive

medications for 4 weeks led to a prevalence of albuminuria of 8%. In another study invovling around 1041 individuals a prevalence of around 6% was observed. The individuals in this study were young individuals with untreated mild hypertension[11]. The LIFE(losartan intervention for endpoint reduction in hypertension) study involving around 8029 patients with stage II-III hypertension the observed prevalence was 26%. In another study with a cohort of 376 hypertensives who were untreated with albuminuria defined as more than 30mg/24hours.the prevalence was 6% for those with albumuria alone and 27% had Left ventricular hypertrophy along with microalbuminria. Overall albuminuria was present in 16% of the patients. It was also suggested from this study that albuminuria is a good ptrdictor of LVH. Significant proportion of long term smokers had both LVH and microalbuminuria than non smokers.

Systolic arterial pressure is a major determinant of microalbuminuria. The relationship between these two is steeper in men than in women. The relationship between left ventricle and systolic arterial blood pressure is somewhat linear. Factors such as diabetes and oral contraception influences this relationship[11]. Various studies have observed that increase in dietary sodium was associated with an increase in steepness of the slope of the

relationship between systolic arterial blood pressure , left ventricular mass index or AER.

Apart from systolic arterial blood pressure smoking, insulin resistence and obesity were shown to be associated with a high level of urinary microalbumin. Studies have also shown that albuminuria is also linked to metabolic syndrome[(11)]. According to adult treatment panel 3 the prevalence of albuminuria was higher in those with metabolic syndrome. It was also found that albuminuria increased the number of components of metabolic syndrome of metabolic syndrome.

In a study conducted by groningen cohort in was observed that increasing C-reactive protein values was associated with remarkable steepening of the slope of relationship between albuminuria and mean arterial pressure.

Many studies have also found that plama homocysteine levels were inversely related to glomerular filtration rate. The higher the level of plasma homocysteine, the lower was the glomerular filtration rate[(11)].

In a study condcuted in patients with mild hypertension it was observed with the angiotensin converting enzyme inhibitor

enalapril when given for over 12 months brought about a significant reduction in albuminuria. This effect was more when compared with othe group of drugs like beta blockers, calcium channel blockers,etc. In LIFE study it was found that losartan brought about a significant reduction in albuminuria when compared to beta blockers. This suggests that prevention of end organ damage was equally important as reduction of blood pressure[11].

Interestingly in a study by redon st al it was shown that in a group of 187 untreated systemic hypertension individuals even after followup and treatment with angiotensin converting enzyme inhibitors and other classes of drugs there was progression from normoalbuminuric to microalbuminuric status. This progression was less in individuals treated with angiotensin converting enzyme inhibtors. Some of the albuminuria progressors are obesity, high blood glucose, high blood pressure, insulin resistance and high uric acid levels.

In the prevention of renal and vascular end stage disease study it was observed that GFR was elevated in patients with high normal urinary albumin (15 to 30mg/ dl) when it was estimated by 24 hour creatinine clearance[11]. Macroalbuminuria was associated with

reduction in creatinine clearance. In another italian study conducted with 1600 subjects no relation ship was found between increasing urine albumin and low creatinine clearance. In the prevention of renal and vascular end stage disease study a de novo development of low creatinine clearance(< 60ml/min/1.73m2) was observed in 4.2 % of the individuals. A multivariate analysis showed that urine microalbumin was a good predictor of the risk of developing renal insufficiency[11].

Another study showed that there was a direct relationship between increasing urine albumin and the decline in GFR as estimated by cockroft gault equation.

No difference in glomerular filtration rate was found between normoalbuminuric and microalbuminuric individuals with systemic hypertension. Even an increasing filtration fraction was not detected. The vasodilatory response to the administration of angiotensin converting enzyme inhibitor captoprin was reduced in patients with microalbuminuria. This suggests that microalbuminuria may be marker of early renovascular dysfunction. It is unknown whether it is the microalbuminuria or the hyperfiltration is a precursor for further renal alterations[11].

Glomerular filtration rate progressively reduces with advancing age.many factors accelrate this decline in glomerular filtration rate. It was found by many studies that presence of a concentric left ventricular hypertrophy is associated with an increased acceleration of age related glomerular filtration rate[11]. This similar acceleration was also found those with glucose intolerance or diabetes.

In a study involving 141 patients the decrease in 24 hour creatinine clearance after 7 years of followup was 12.1ml/min in microalbuminuric and 7.7ml/min in normoalbuminuric hypertensive patients and the antihypertensive therapy did not have any effect. Interestingly the most signifiant predictor of reduction in glomerular filtration rate over time was blood pressure in most studies.

Microalbumuria is a predictor of cardivascular mortality. Many studies have shown that the urine albumin values that increase the cardiovascular risk were lower than the cut off values that are established for the criteria for microalbuminuria. Similar is the case for urine albumin creatinine ratio[11]. Studies have shown that in people aged more that 40 years the cardiovascular risk was high for albumin creatinine ratios of 1.28 to 2mg/mmol. In another study the threshold of urinary albumin creatinine ratio was 0.65mg/mmol

creatinine roughly corresponding to an urinary albumin of 5-6 micro g/min. Another study has demonstrated that microalbuminuria and peripheral arterial disease were associated with a four fold rise in cardiovascular mortality. This rise was more significant for hypertensive subjects when compared to normotensive subjects. This study concluded that microalbuminuria brought about a rise in cardiovascular mortality through a different mechanism than extensive atherosclerosis[11].

Many studies have looked in to the relationship between renal outcomes and microalbuminuria in type 2 diabetic populations.

It is shown by many studies that in patients with urinary albumin concentrations of 30 to 140 Mg/ml more likely developed clinically detectable levels of proteinuria (>400 Mg/ml) after a followup period of 9 years. These findings were supported by another study by berrut et al who examined patients with type 2 diabetes and systemic hypertension. The glomerular filtration rate fall was more in patients with microalbimunuria than normoalnuminuria[11].

In a study that exmained 1715 patients with hypertension, dibetes and proteinuria called the irbesartan diabteic nephropathy trial the risk of developing end stage renal failure or the doubling of the serum creatinine

concentration occured in those indivduals with doubling of proteinuria. The individuals included in this study were people with urinary protein of altleast 900mg/24hours and a baseline serum creatinine level of 1.0 and 3.0mg/dl[11].

In another study called the reduction of end points in non-insulin dependent diabtes mellitus with angiotensin II antagonist losartan study which included a population of 1513 patients with diabetes type 2 and nephropathy(defined as urinary albumin creatinine ratio of >300mg/g and a serum creatinine of 1.0 to 3.0 mg/dl it was observed that presence of albuminuria increased the risk of end stage renal disease.

A metanalysis has also demonatrated that microalbuminuria is a potential risk factor for the development of preogressive kidney disease.

Several studies have showed that bringing down urine albumin levels by inhibiting the renin angiotensin system by drugs results in prevention on further detoritaiton and preserving of renal function[11].

The reduction of end points in non-insulin dependent diabetes mellitus with angiotensin antagonist losartan trail showed that adding losartan to anti hypertensives taken by anti hypertensive patients resulted in reduction of proteinuria 35 % more than in placebo cases. A 50%

reduction in albumin level resulted in the reduction in the risk for end stage renal failure by 45%[11].

Similarly in IDNT trial which included 1715 patients with type 2 diabetes and systemic hypertension it was showed that irbesartan caused a significant reduction in the risk of serum creatinine doubling when compared to the placebo group. It also caused a 23% reduction in the risk of progression to end stage renal failure.

For a 50% reduction in the level of urine albumin excretion the risk of doubling of serum creatinine and the progression to end stage renal failure was brought down by 50%.

Both angiotensin converting enzyme inhibitors and angiotensin receptor blockers achieve this reduction in urinalry albumin by reducing the intraglomerular pressure thus reducing the filtration.

The microalbuminuria reduction with valsartan study also showed a similar result (urinary albumin excretion rate was 56% at 24 weeks for valsartan and 92 % for amlodipine). However blood pressure reductions were similar in the two groups[11]. Thus the angiotensin receptor blockers are very beneficial in preserving renal function and improve renal outcomes. Increasing the dose of the angiotensin recetor blocker further

improves the renal outcome which is independent of blood pressure control.

The irbesartan in patients with type2 diabetes and microalbuminuria study showed that risk of progression to nephropathy was significantly less with using 300mg of irbesartan when compared to 150mg of irbesartan[11]. The result was achieved after adjusment for the baseline blood pressure and microalbuminuria achieved during the study. Given these results studies are now going on find out whether doses beyond recommended doses can bring about greater reno vascular protection.

Other potential ways to increase the inhibition of renin angiotensin system apart from increasing the dose of angiotensin converting enzyme inhibitors and angiotensin receptor blockers is to add an aldosterone inhibitor such as spironolactone or eplerenone.

A strong association exists between microalbuminuria and cardiovascular outcomes in diabtes mellitus type 2. In the heart outcomes prevention evaluation study which studied 5545 patients without diabetes and 3498 patients with diabetes showed that the increased urinary albumin increased the relative risk of cardiovascular events. Type 2 diabetic people had a relative risk of 1.83 where as the non diabetic people had a relative risk of 1.61[11].

Albuminuria is an independent risk factor for major cardiovasculr events this was demonstrated by the IDNT study. The cardiovascular end point in this study were cardi0vascular death, hospitalization for heart failure, amputation, cerebrovascular accidents, peripheral and coronary revascularisation and non fatal myocardial infarction[11].

The urinary albumin creatinine ratio was associated with increased risk of these cardiovascular endpoints. The reduction of endpoints in non-insulin dependent diabetes mellitus with angiotensin II antagonist losartan study aslo demonstrated that increased urine albumin was associated with increased adverse cardiovascular events. According to this study the cardiovascular events were defined as composite of cerebrovascular events, first hospitalisation for unstable angina, first hopsitalisation for heart failure, peripheral revascularisation, coronary revsacularisation, myocardial infarction[11].

This study also demonstrated that higher the urinary albumin creatinine ratio higher is the risk of cardiovascualar end points for example an individual with a high baseline albumin creatinine ratio (>3g/g) had a 1.92 fold higher risk for adverse cardiovascular events.

Gimerno et al studies 436 patients with diabetes mellitus type 2. He classified these patients in to four categories and he found that patients

with absent cardiovascular disease but higher microalbuminuria had an increased relative risk for cardiovascular disease compared with people who had normal urinary albumin and cardiovascular disease. This study also showed that in patients who had microalbuminuria alone ,the risk of getting a subsequent cardiovascular event was the same as in those who have already experienced a carfdiovascular event[(11)].

Microalbuminuria is also a risk factor for advanced cardiovascular disease. In a study that studies 330 patients with diabetes and microalbuminuria and those without microalbuminuria, it showed that the diabetes with microalbuminuria had a higher prevalence of three vessel disease when compared to those without microalbuminuria. Many lines of studies exist showing that the risk of adverse cardiovascular events increases as the urinary albumin excretion progresses from microalbuminuria to albuminuria and then proteinuria. This has been predominanlty studies in diabetic populations.

Although many studies have widely established that micralbuminuria is a independent risk factor for adverse events in diabetic populations, evidence suggests that the presence of albuminuria is a potent risk factor for adverse cardiovascular events in non-diabetic populations as well[(11)].

Im framingham study which studied around 1568 non hypertensive patients who did not have diabetes mellitus it was shown that urine albumin levels less than the microalbuminuria threshold predicted the risk of adverse cardiovascular events[11]. In prevention of renal and vascular end stage disease study which was conducted in 6669 nondiabteic participants it was shown that microalbuminuria increases the cardiovascular disease risk. Some studies have also suggested that the relative risk of an adverse cardiovascular event is also increased by microalbuminuria similar to high cholesterol levels. Thus the microalbuminuria must be viewed with a similar weightage given to other cardiovascular risk factors such as high blood sugar, hypercholesterolemia and systemic hypertension.

The prevention of renal and vascular end stage disease showed that the usage of fosinopril brought about a significant 26% reduction in urine albumin excretion and thus the risk of adverse cardiovascular events. In life study it was demonstrated that reduction in urinary albumin creatinine ratio reduced the risk for cardiovascular mortality. And thus these observations strongly suggest that high urine albumin levels are independent predictoes of cardiovascular events and a reduction in their level greatly reduces cardiovascular mortality[11].

SMOKING AND THE KIDNEY

POTENTIAL MECHANISMS:-

Chronic smoking increases the progression of nephropathies. It increases the progression from microalbuminuria to macroalbuminuria and then on to progressive renal failure in diabetic population. In a large study the prevalence of micro and macroalbuminuria was higher in smokers when compared to non smokers with diabetes mellitus type II. In a study conducted in patients with polycystic kidney disease the proteinuria was higher in patients who were smokers[(4)].

The time period between median and end stage disease was shorter in smokers when compared to non-smokers in patients with lupus nephritis. In a study conducted among patients with IgA nephropathy and polycystic kidney disease it was found that smoking increased the progression to end stage disease if they had not received angiotensin converting enzyme inhibitors. This suggests that smoking is a modifiable factor in diabetic and non-diabetic populations.
The effects smoking in people without preexisting disease conditions have not been well studied. In study with 24 apparently normal smokers and 30 non smokers it was shown that smokers had reduced renal plasma flow which was assessed with 51CR-EDTA clearance[(4)]. Another study

showed that smoking 120 insulin dependent diabetes patients had higher glomerular filtration rates than their non-smoking counterparts. Smoking was associated with high urine albumin excretion rates in hypertensive patients. Untreated hypertensive smoking pateints had a two fold higher prevalence of microalbuminuria when compared to non smokers. The most important factor which determines the microalbuminuria is the arterial blood pressure[(4)].

In hypertensive patients the reason for microalbuminuria is believed to be the transglomerular passage of albumin in most patients. The exception to this is primary hyperaldosternism. Hypertensive smokers with microalbuminuria have a faster decrease in creatinine clearance when compared to normoalbuminuric patients.

Acute effects of smoking differ with the duration of smoking, habit of smoking and with underlying pathology. For example one study has demonstrated that oral nicotine administration caused a marked and proportional decrease in renal plasma flow and glomerular filtration rate in those who have never smoked before where as the same administration caused no change in renal plasma flow in chronic smokers[(4)]. Contradicting this another study has shown that acute smoking brought about a reduction in glomerular filtration rate but did not reduce renal plasma flow in individuals who were occasional smokers. Another study

demonstrated that acute smoking did not bring about a change in glomerular filtration rate in patients with IgA nephropathy. It appears that the acute effect of smoking depends on the type of smoking habit[4].

Arterial pressure rises transiently during and after smoking due to the surge of catecholamines. Many studies have shown that as a result of this phenomenon smokers are at increased risk of developing malignant hypertension when compared to non-smokers. Another effect that smoking brings about is a rise in endothelin levels. Other that rise include vasopressin,ACTH, thromboxane, etc and all of these play a role in progression of nephropathy.

Smoking leads to an excessive production of free radical and thus oxidative stress and the condition is worsened by the reduced levels of ascorbic acid in chronic smokers. Smokers exhibit abnormal endothelin mediated vasodilatation in response to nitrates or acetylcholine due to endothelial damage brought about by the free radicals. This response improved when ascorbic acid was supplemented. one study demonstrated that non smokers who were given nicotine gum exhibited low urinary levels urinary cGMP which meant low nitric oxide production[4].

Smoking affects the autonomic nervous system by bringing about adrenaline and nor adrenaline release which leads to acute rise in blood pressures[4].

Effects of smoking in the general population:-

Smoking leads to a increase in urinary albumin excretion. Smoking was independently linked with increased albumin excretion rates even in nondiabetic normotensive populations. A cross sectional study which was done in 7476 non-diabetic individuals showed that albumin excretion rates correlated with increasing pack years and that there was a dependent association. Smoking increases the risk of detoriation of renal function apart from causing increased albumin excretion. Smoking increases creatinine clearence among smokers but the effect is limited to current smokers and it reverses among cessation of smoking. Some Studies have also found a dose dependent increase of the risk of end stage renal failure in smokers[4].

A prospective study which studied 4142 individuals above age 64 years showed that smoking contributed to the doubling of serum creatinine over a 3 year time period. Smoking can explain why renal deterioration occurs not in all but only in some people.

Effect of smoking on patients with primary hypertension:-

10-25 % of patients with primary hypertension exhibit albuminuria and 4-18% of patients with primary hypertension exhibit proteinutria. Smoking is an independent predictor for microalbuminuria in patients with essential hypertension. This was showed by the heart outcomes and prevention study[(2)]. Another study has found that patients with left ventricular hypertrophy, smoking history and hypetension had higher prevalence of microalbuminuria when compared to non-smokers.

Regalado et al did a prospective study with 51 patients of hypertension. These 51 patients were followed up for a period of 35 months. And he found that increase in serum creatinine occurred despite adequate control of blood pressure. This study showed that there were independent factors which predicted renal detoriation and they were black ethnicity, higher initial base line serum creatinine and smoking. And the most strongest predictor among these was smoking.

Effects of smoking in patients with renal disease:-

First report that smokers had a higher risk to develop diebetic nephropathy came from a study that was conduucted way back in 1978[(2)]. This was later confirmed by another study which incuded 668 type 1 diabetic individuals. Nephropathy was present in around 13% of the

people who smoked <10 cigarettes per day whereas it was present in >25% in people who smoked more than 30 cigarettes per day[2]. There after many studies were done in type II diabetes mellitus populations and a similar result was obtained. The adverse effect that smoking produced on the kidney did not depend upon the age or duration of the disease. And this was applicable to both type 1 and type 2 diabetes patients. Another study also demonstrated that urinary albumin levels were higher among diabetic patients who were smokers. The same study also demonstrated that the risk of microalbuminuria was high in the first few months following the diagnosis of diabetes mellitus. In another study which included 794 individuals showed that dibetic patients who were smokers had a higher relative risk for the progression of microalbuminuria to overt proteinuria when compared to their nonsmoking counterparts.

Another study by sawicki showed the odds ratio for the progression of diabteic nephropathy defined as a >20% rise in proteinuria and >20% fall in glomerular filtration rate with every 10 pack years was 2.74 when compared to non-smokers. Diabetes mellitus patients reach end stage renal failure faster when compared to people fo other groups[2].

Another study which studied 16 patients with type 2 diabetes and 16 patients with type 1 diabtes showed that the rate of decline in creatinine clearance at the end of the study was greater in smokers when compared

to non-smokers. The rate of decline in smoking patients with diabetes mellitus type 2 was 1.21 and in those who were non smokers was 0.73. rate of fall in glomerular filtration rate was approximately 56% higher in smoking individuals when compared to non-smoking individuals[(2)].

Another propective study conducted by chuahirun and wesson revealed more information regarding the effect of smoking in diabetes mellitus type 2 patients. In this study blood pressure was well controlled according to current standards, glycemic control was also good. At the end of this study the rise in serum creatinine was significanlty higher in smokers when compared to nonsmokers. In this study there were no other confounding factors and so smoking was the only factor which caused a rise in creatinine. Some retrospective and prospective studies have shown that angiotensin converting enzyme inhibitors provide reno protection in smoking induced renal damage by way of improving endothelial function after angiotensin converting enzyme inhibition. Some of the beneficial effect of angiotensin converting enzyme inhibition include scavenging of free radicals and removing the cigarette induced suppression of nitric oxide[(2)]. Thus smoking clearly has adverse effects on both type 1 and type 2 diabetes individuals.

Smoking also affects the progression of non diabetic renal disease. This was first suggested by a study on patients with autosomal dominnant

polycystic kidney disease. Then on studies were also done involving people with IgA glomerulonephritis[2]. These studies suggested that the rate of progression to end stage renal failure increased in male smokers compared with non smokers and the risk was substantially high in patients who did not have a history of treatment with angiotensin converting enzyme inhibitors. The reduction in glomerular filtration rate was 5.3ml/min in heavy smokers and was only 2.3ml/min in non smokers over a 3 year follow up. This shows that the smoking status is related to the rate of decrease in glomerular filtration rate. Smoking doubles the rate of progression of chronic glomerulonephritis. Studies among women do not exist widely and in one study which included 246 patients with type1 diabetes mellituts no relation ship was found between smoking and diabetic nephropathy progression and ofcourse large scale studies are needed in women.

Only limited studies are available regarding the effects of smoking on the renal disease that occur as a result of systemic diseases. One retrospective study which included around 160 patients with lupus nephritis showed that smoking was an independent and strong predictor for the progression to end stage renal failure[2]. The effect of smoking was not dependent on the type of immunosuppressive treatment given to these patients or the presence of hypertension in these patients.

One other study also suggests that smoking induced endothelial damage might pave the way for the formation of antibodies against nuclear antigens released from endothelial cells and thus these can lead to the development of ANCA positive glomerulonephritis. Smoking also increases the risk of alveolar hemorrhage in good pasture syndrome patients[(2)].

Potential mechanisms of smoking induced injury:-

1) Rise in sympathetic activity.
2) Rise in arterial blood pressure and heart rate
3) Circadian fall in blood pressure during night time is affected
4) Renal vascular resistance is increased due to reduced renal blood flow.
5) Rise in intraglomerular pressure
6) Increased hyperfiltration in patients with diabetes
7) Renal artery atherosclerosis and myointimal hyperplasia of renal vascualture
8) Endothelin and angiotensin mediated proliferation of mesangial, endothelial and vascular smooth muscle cells[(2)].
9) Toxic effects on the renal tubules
10) Toxic effects on endothelium such as

➔ Altered thromboxane and prostagalndin metabolism

➔ Oxidative stress created by free radicals

➔ Reduced nitric oxide levels

➔ Dysfunctional vascular dilatation

➔ Monocyte adhesion to endothelium is increased.

➔ Hypoxia due to carbon monoxide production

11) Increased aggregation of platelets

12) Dysfucntional glycosaminoglycan and lipoprotein metabolism

13) Immune dysregulation

14) Increased anti-diuresis due to increased vasopressin release.

15) Development of insulin resistance.

Smoking and renal artery atherosclerosis:-

Smokers have a higher prevalence of peripheral vascular disease and renal vascular stenosis occurs with a higher prevalence in those with peripheral vascular disease. Predominant proportion of people with unilateral or bilateral renal artery stenosis are smokers[(2)]. Smoking accelrates the rate of decline in renal function with renal artery stenosis. Apart from damage to the vasculature one another mechanism by promoting cholesterol microembolism. Studies have shown that renal blood flow decreased progressively with increasing severity of peripheral

arterial atherosclerosis. Extra renal atherosclerosis and renal hypoperfusion are closely related[(2)].

Effects of smoking in renal transplant patients:-

A cohort study was conducted in the year of 1985 which included about 645 adult renal allograft recipients. 24% of these patients were smokers. smoking before transplant was associated with reduced graft survival in the post transplant period. Patients who were smokers before tranplant had a graft survival of 48% at the end of 10 years and those who were non smokers had a graft survival of 62% at the end of 10 years. For those who smoked but quit during the transplant evaluation phase, the death censored graft survival was significanlty high when compared to those who did not quit smoking. The reduced survival were not explained by rejection episodes. Thus smoking cesssation has a major impact on graft survival. The extent to which the smoke has impact on the graft may also depend on the preexisting disease condtion that caused that end stage renal failure in the patient. Smoking induced immune dysregulation are particularly detrimental in patients with renal pathology due to immune regulation abnormalities such as systemic lupus erythematosus[(2)].

Reversibility of smoking induced damage:-

Studies have shown that cessation of smoking significantly reduces the urine albumin. Of course it goes without saying that this occurs only with adequate glycemic control and blood pressure control. Another study has shown that progression of renal failure is around 53% in active smokers and in the long run this rate falls down to 33 % after smoking cessation[(2)]. This is also applicable to non-diabetic renal disease. Risk of microalbuminuria in significant in active smokers and it is very mild in those who have stopped smoking. The reduction in renal blood flow however is not completely reversible following smoking cessation. Pharmacological therapies available for smoking cessation are nicotine in its various forms like patches, gums, sprays, bupropion(dopamine and noradrenaline reuptake inhibitor), varenicline (partial agonist of nicotinic acetyl cholinergic receptors, clonidine, anxiolytics such as beta blockers, benzodiazepines, buspirone, anorectics like fenfluramine and phenylpropanolamine and stimulants such as amphetamines and methylphenidate.

MATERIALS AND METHODS

STUDY POPULATION:

This study was conducted in 120 non-diabetic, normotensive and non-obese subjects who were attending the general medicine outpatient clinic at government rajaji hospital, Madurai. Out of the 120 patients, 76 were smokers and 44 were non-smokers.

CONTROL POPULATION

Out of the 120 patients, 76 were smokers and 44 non non-smokers. The non-smokers were age matched and taken as control group.

Inclusion criteria:

1) Age 30 to 70 years.
2) Normotensive (≤139/≤89 mmHg)
3) Non-obese (body mass index (BMI <30 Kg/m2)
4) No family history of premature vascular disease
5) Normal total cholesterol (<200 mg/dl)
6) Normal renal function (urea ≤40 mg/dl and creatinine ≤1mg/dl)
7) Not on any regular cardiovascular medication and given informed consent. Clinically stable.

Exclusion Criteria:

1) age < 30 years and > 70 years.
2) Diabetes mellitus/ using insulin or hypoglycemic agents.
3) Hypertensives or using anti-hypertensive medications.
4) Hyperlipidemic or using lipid lowering drugs.
5) Obese (BMI ≥30 Kg/m2)
6) Abnormal renal parameters.
7) Urinary tract infection.
8) Significant renal disease or using diuretic drugs.
9) Angiotensin converting enzyme inhibitors.
10) Alcohol consumption or other significant drugs.
11) Fever
12) Vigorous physical activity
13) Not willing to give consent.

PERIOD OF STUDY : JUNE 2014 TO SEPTEMBER 2014.

TYPE OF STUDY : analytical Cross sectional study

PARENT DEPARTMENT : Department of General Medicine.

COLLABORATING	:	Department of nephrology and
DEPARTMENTS		Department of biochemistry
ETHICAL CLEARANCE	:	Obtained
CONSENT	:	Individual informed consent.
ANALYSIS	:	STATISTICAL ANALYSIS
CONFLICT OF INTEREST	:	NIL
FINANCIAL SUPPORT	:	NIL

PARTICIPANTS:

120 non-diabetic, normotensive and non-obese subjects were included in this study from the general medicine outpatient clinic. A brief history and clinical examination were done. Smokers were defined as those who have smoked atleast 20 bidi /day for 5 years (5 pack years) or equivalent.

smokers were classified in to four groups:-

1) very light smokers → 5-9 pack years
2) light smokers → 10-14 pack years

3) moderate smokers → 15-19 pack years
4) heavy smokers → >20 pack years.

Out of 120 subjects in our study 76 (63.3%) were smokers and 44(36.7%) were non-smokers. All were males. The 44 non smokers were age matched and taken as control. The baseline physical characteristics and biochemical characteristics of these two groups were compared used statistical tests.

LABORATORY INVESTIGATIONS :

overnight fasting blood sugar, serum creatinine, serum urea and lipid profile were measured. The blood sugar was measured using the glucose oxidase and peroxidase method. Serum urea was measured using the enzymatic glutamate dehydrogenase method. Serum and urine creatinine concentrations were measured using the jaffe's calorimetric method. The urine albumin was measured using turbidimetric method from first morning void (timed) mid stream urine samples. Since the turbidimetric method and the timed urine sample was used for urine albumin measurement the cut off value for microalbuminuria in this study is taken as 20 mg/L. In lipid profile total cholesterol was measured using the cholesterol oxidase peroxidase method. The triglyceride was measured using the glucose 3 phosphate oxidase-peroxidase method. Cholesterol in the supernatant is measured after precipitation of apo-B containing

lipoprotein by polyethylene glycol to determine the HDL cholesterol. LDL cholesterol is estimated by using the friedewald formula and this formula appears to be the most practical and reliable method for determining LDL-cholesterol in clinical practice.

LDL cholesterol=Total cholesterol-[HDL+(Triglyceride/5)]

VLDL is estimated by dividing the plasma triglyceride by 5 reflecting the ratio of cholesterol to triglyceride in VLDL particles.

After obtaining the results, the data was compiled in a Microsoft Excel sheet. Statistical analysis was done using IBM SPSS Ver.16 (Statistical package for social sciences). Percentage prevalence, Standard deviation and 'p' values were calculated. Chi – Square test and Student t test were used to find out the significance of relationship between cases and controls.

Limitations of the study:

1. small number of subjects.

2. single centre study.

3. only the one timed urine sample was used.

4. Direct LDL measurement was not done, derived by friedwald formula

RESULTS AND INTERPRETATION

After applying the inclusion and exclusion criteria 120 cases were selected for the study. The age distribution is as follows,

Table 1: Age distribution of the study population(n=120)

AGE GROUP	SMOKERS (n=76)	NON-SMOKERS (n=44)	TOTAL (n=120)
30-40 years	12 (15.78%)	8 (18.18%)	20
41-50 years	35 (46.05%)	24 (54.54)%	59
51-60 years	27 (35.52%)	11 (25%)	38
61-70 years	2 (2.63%)	1 (2.27%)	3
TOTAL	76	44	120

Mean age:- 47.27 S.D:- 6.553

Maximum:- 64

Minimum:-33

The p value comparing the two means of the study and control group was 0.169 and hence the two groups are comparable with respect to age.

CHART 1:- AGE DISTRIBUTION

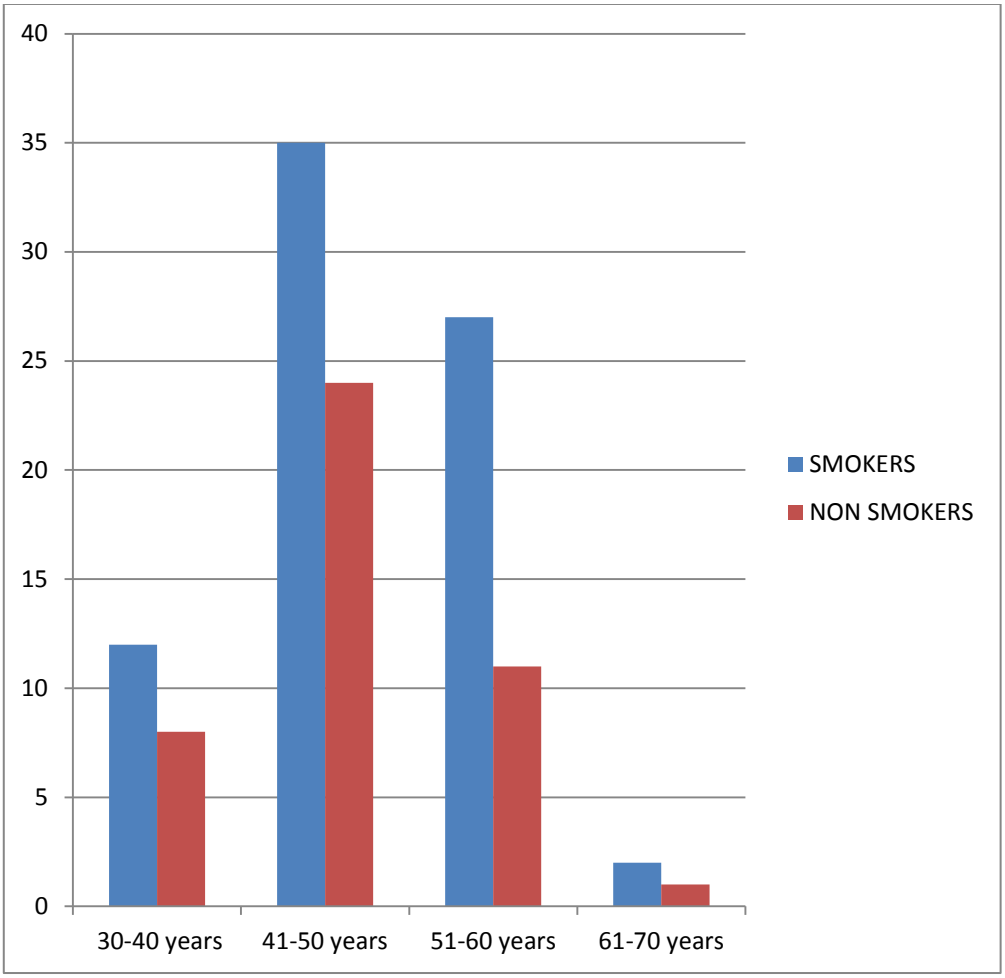


Table 2 .Distribution of the study population according to study & control groups (n=120)

	Frequency	Percent	Valid Percent	Cumulative Percent
SMOKERS	76	63.3	63.3	63.3
NON SMOKERS	44	36.7	36.7	100.0
Total	120	100.0	100.0	

Table 3. Distribution of smokers according to pack years

5-9 pack years	45 (59.21%)
10-14 pack years	15 (19.73%)
15-19 pack years	12 (15.78%)
More than 20 pack years	4 (5.26%)
Total	76

CHART 2. Distribution of smokers according to pack years

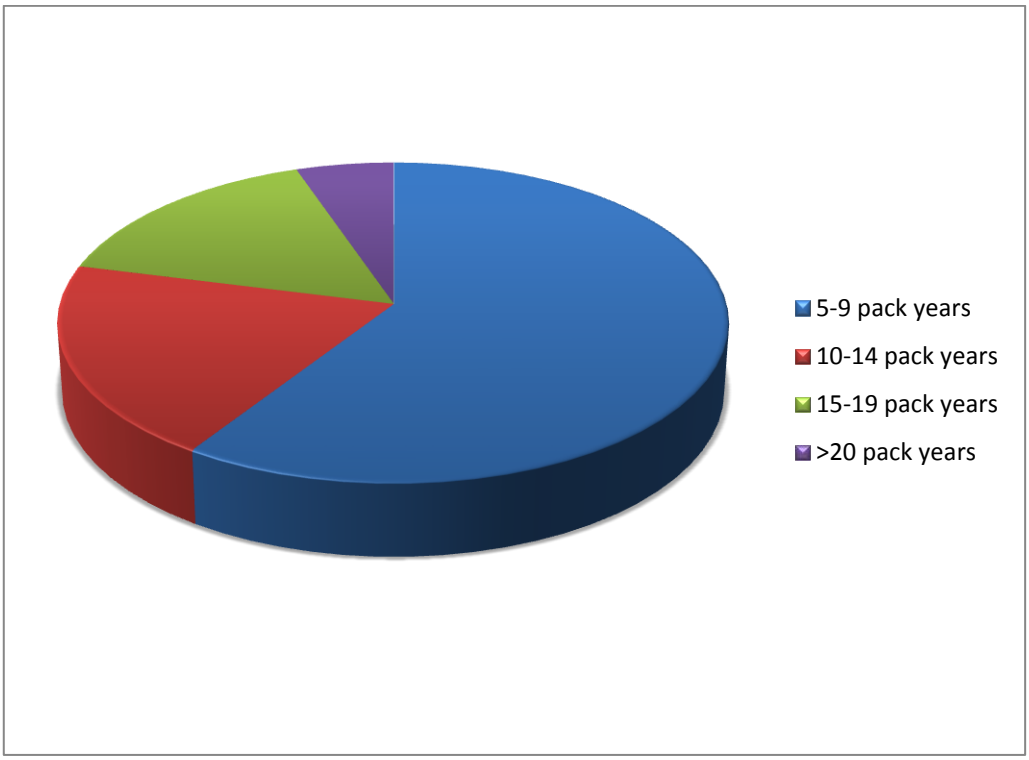


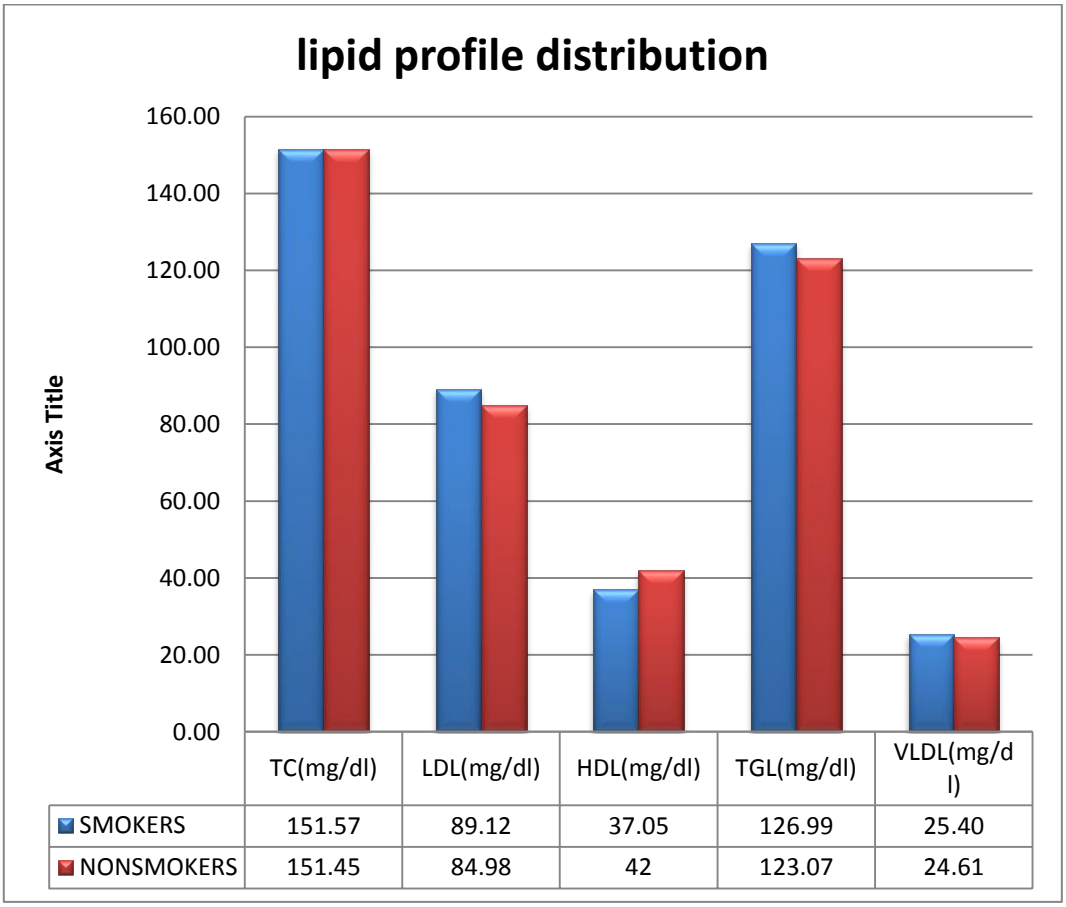
TABLE 4. Descriptive statistics of the biochemical and physical parameters between smokers and non-smokers

Variable	Mean		S.D	Minimum	maximum
	smokers	Non-smokers			
BMI	22.128	22.525	1.1176	18.9	24.7
SBP (mm Hg)	124.16	123.73	4.0000	114	132
DBP (mm Hg)	75.50	75.61	3.569	70	82
FBS (mg/dl)	84.95	83.55	6.687	72	98
TC (mg/dl)	151.62	151.45	4.419	144	163
LDL (mg/dl)	89.116	84.977	4.978	75	98
HDL (mg/dl	37.05	42.00	3.835	30	56
TG (mg/dl)	126.99	123.07	8.500	113	150
VLDL (mg/dl)	25.397	24.614	1.69	22.6	30
SERUM UREA(mg/dl)	24.46	25.39	4.637	17	34
SERUM CREATININE (mg/dl)	0.750	0.745	0.0622	0.6	0.9
CREATININE CLEARANCE (ml/min/1.72m2)	102.310	105.355	8.3098	76.5	123.0

TABLE 5. Independent samples test for physical and biochemical parameters.

characteristic	P value	95% confidence interval	
		lower	Upper
BMI	0.060	-0.8119	0.176
SBP (mm Hg)	0.572	-1.074	1.935
DBP (mm Hg)	0.867	-1.458	1.231
FBS (mg/dl)	0.270	-1.104	3.908
TC (mg/dl)	0.846	-1.501	1.828
LDL (mg/dl)	<0.001	-5.7234	-2.5536
HDL (mg/dl	0.001	-6.076	-3.819
TG (mg/dl)	0.014	0.797	7.040
VLDL (mg/dl)	0.014	-1.4080	-0.1595
SERUM UREA(mg/dl)	0.294	-2.665	0.813
SERUM CREATININE (mg/dl)	0.701	-0.189	0.0279
CREATININE CLEARANCE (ml/min/1.72m2)	0.535	-6.1257	0.0360

GRAPH 3. Distribution of lipid profile among the study population.



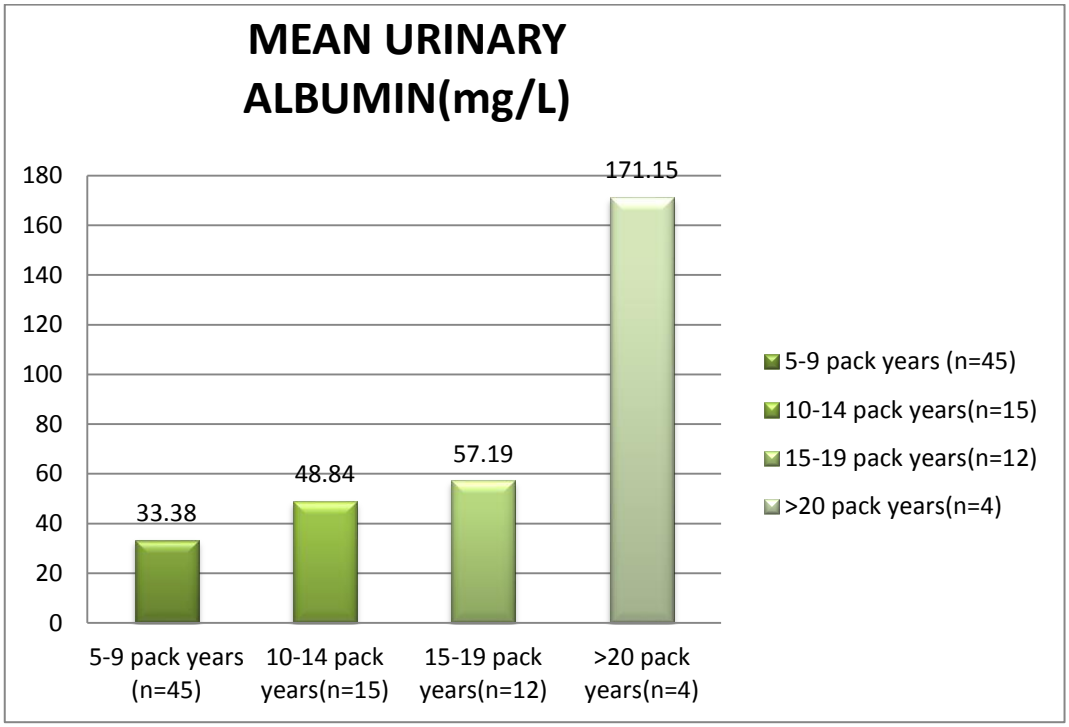
	TC(mg/dl)	LDL(mg/dl)	HDL(mg/dl)	TGL(mg/dl)	VLDL(mg/dl)
SMOKERS	151.57	89.12	37.05	126.99	25.40
NONSMOKERS	151.45	84.98	42	123.07	24.61

In this study smokers had significantly low HDL levels to non-smokers. p value was 0.01 and so the difference in HDL between the smokers and non-smokers was statistically significant.

TABLE 6. Distribution of microalbuminuria in mg/L among the study population

			MICROALBUMINURIA CATEGORY		
			<20	>20	Total
GROUP	Smokers	Count	7	69	76
		% within GROUP	9.2%	90.8%	100.0%
	Non-smokers	Count	37	7	44
		% within GROUP	84.1%	15.9%	100.0%
Total		Count	44	76	120
		% within GROUP	36.7%	63.3%	100.0%

GRAPH 4.Graph showing the distribution of microalbuminuria among the study population.

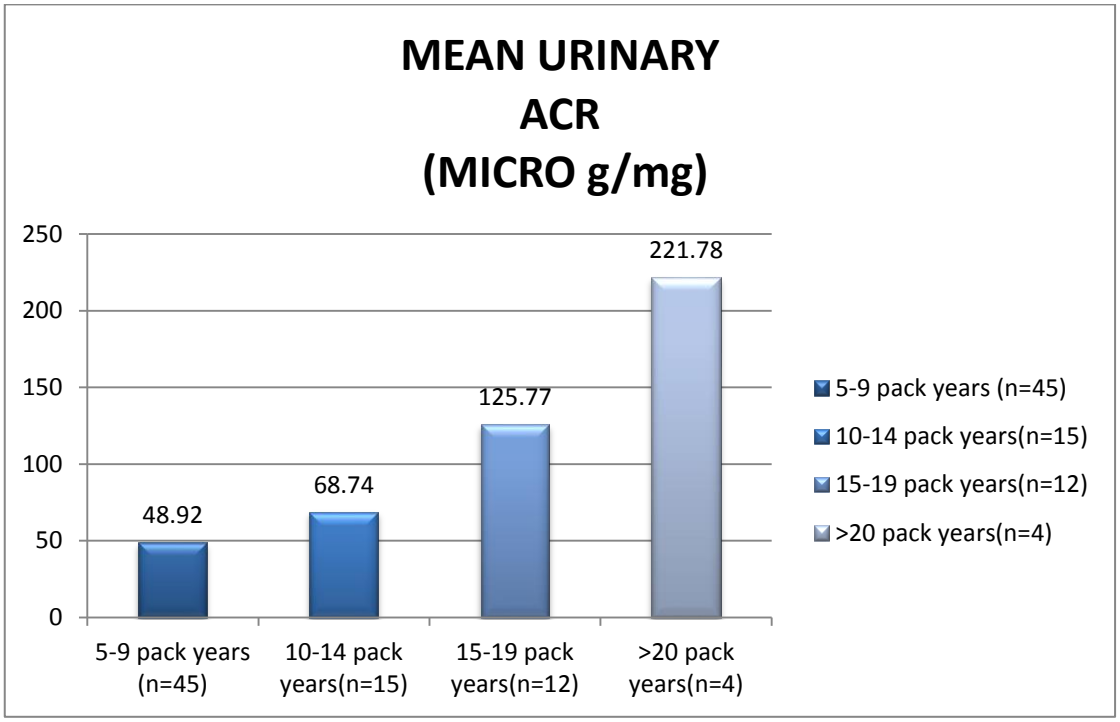


PACK YEARS	MEAN URINARY ALBUMIN (mg/L)
5-9 pack years (n=45)	33.38
10-14 pack years (n=15)	48.84
15-19 pack years (n=12)	57.19
>20 pack years (n=4)	171.15

TABLE 7. Distribution of mean urine albumin creatinine ratio (ACR) in micro g/mg

			ACR CATEGORY		
			<30	>=30	Total
GROUP	SMOKERS	Count	13	63	76
		% within GROUP	17.1%	82.9%	100.0%
	NONSMOKERS	Count	42	2	44
		% within GROUP	95.5%	4.5%	100.0%
Total		Count	55	65	120
		% within GROUP	45.8%	54.2%	100.0%

GRAPH 5. Graph showing the distribution of mean urinary albumin creatinine ratio.



PACK YEARS	MEAN URINE ACR (micro g/mg)
5-9 pack years (n=45)	48.92
10-14 pack years (n=15)	68.74
15-19 pack years (n=12)	125.77
>20 pack years (n=4)	221.78

TABLE 8. Comparison between mean urine albumin between smokers and non-smokers.

GROUP	N	Mean	Std. Deviation	P value	95% confidence interval
smokers	76	47.3271	31.52392	<0.001	18.82491-37.94884
Non-smokers	44	18.9402	7.04755		

The chi square test p value was <0.001 comparing the means of both smokers and non-smokers and hence the difference is significant.

GRAPH.6 showing the comparison of mean urinary albumin between smokers and non-smokers

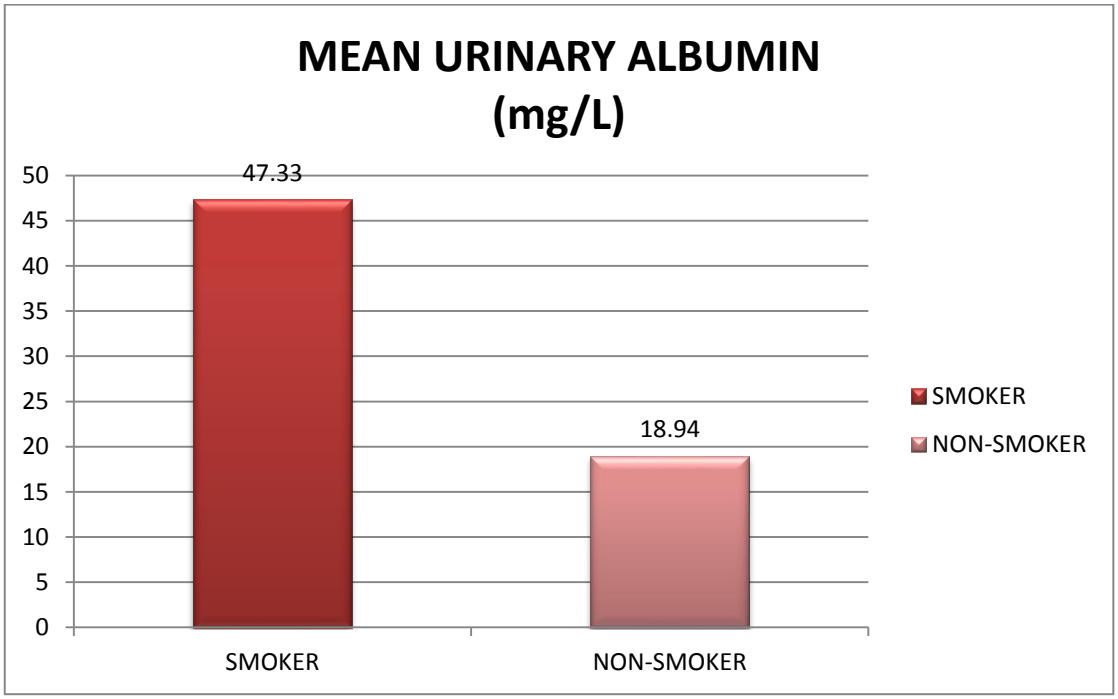


TABLE 9. comparison of mean urinary albumin creatinine ratio between smokers and non-smokers.

	GROUP	N	Mean	Std. Deviation	P value	95% confidence interval
URINE ACR (micro g/mg)	smokers	76	74.0617	49.95803	<0.001	38.42963-68.38061
	Non-smokers	44	20.6566	4.49084		

The chi square p value comparing the two means was <0.001, hence the difference was statistically significant.

Graph.7 showing the comparison of urine ACR between smokers and non-smokers

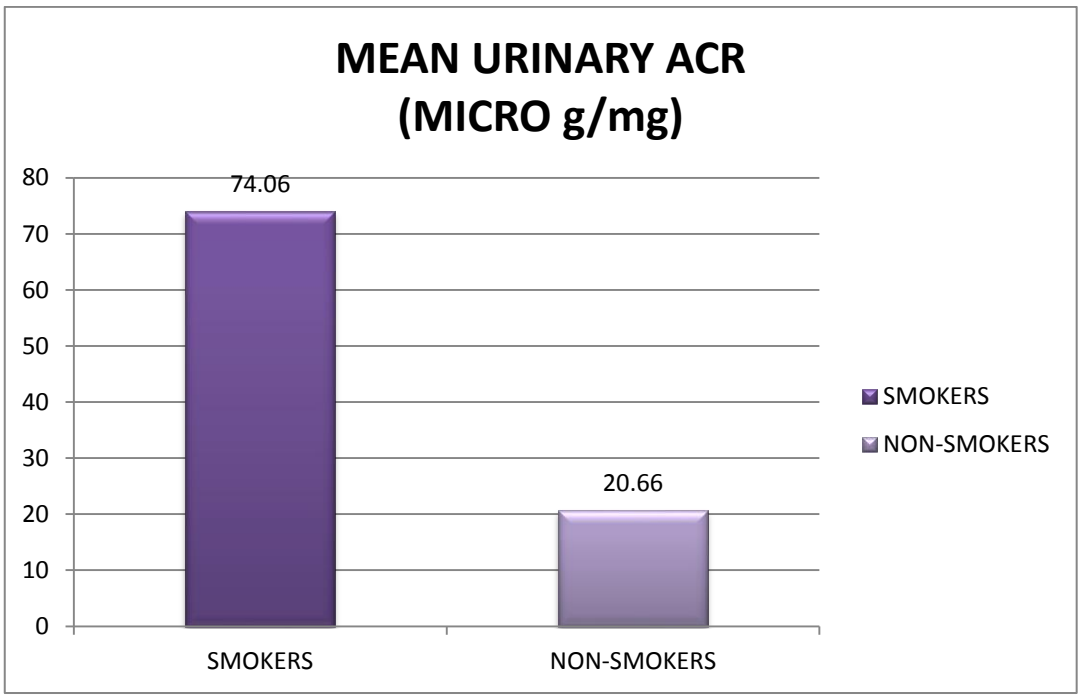
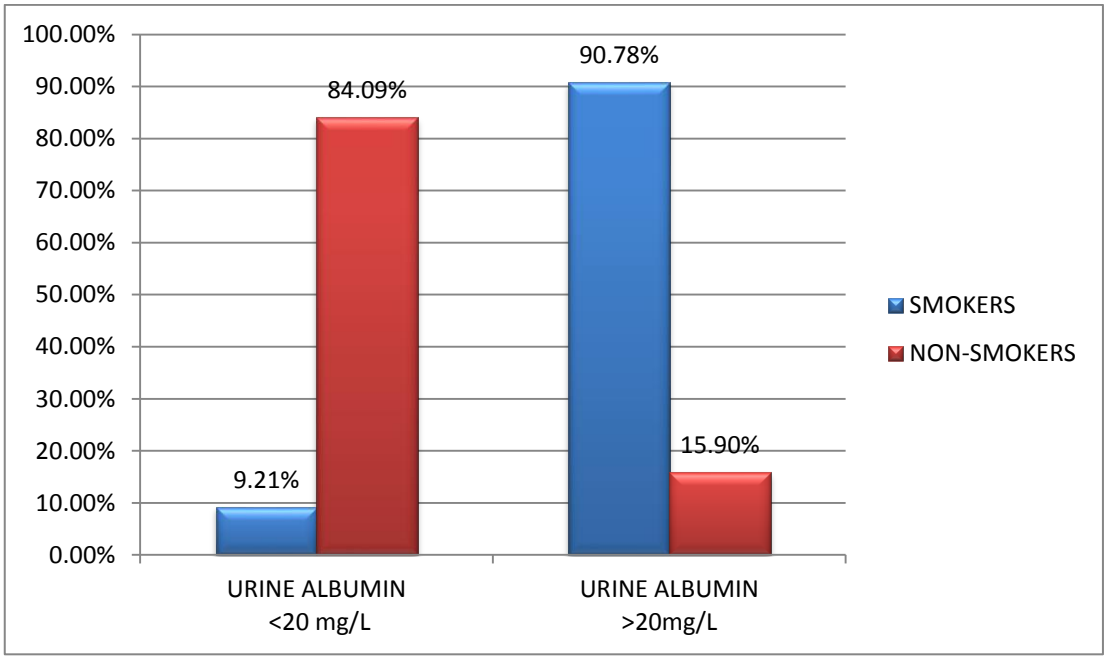


TABLE 10. showing the smoking group descriptive statistics with regard to urine albumin and urine ACR

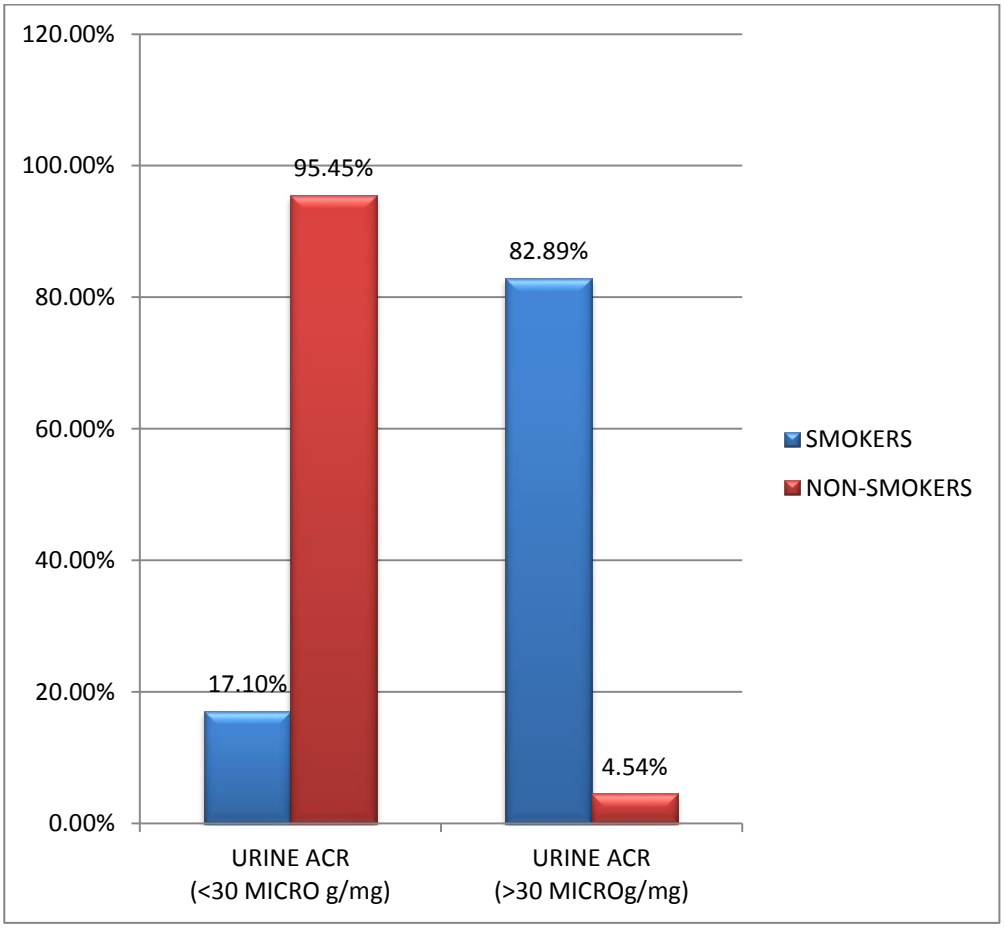
	Pack years	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max
						Lower	Upper		
URINE ACR (micro g/mg)	5-9	45	48.92	17.41	2.59	43.68	54.14	17.65	61.66
	10-14	15	68.74	15.01	3.87	60.42	77.05	23.67	83.64
	15-19	12	125.76	43.51	12.56	98.11	153.41	69.73	186.78
	>=20	4	221.77	23.22	11.61	184.81	258.73	190.56	245.56
	Total	76	74.06	49.95	5.73	62.64	85.47	17.65	245.56
URINE ALBUMIN (mg/L)	5-9	45	33.31	6.54	.97	31.35	35.28	16.35	39.12
	10-14	15	48.44	8.72	2.25	43.61	53.27	17.45	53.56
	15-19	12	57.19	1.11	.32	56.48	57.90	55.67	59.01
	>=20	4	171.14	8.65	4.32	157.37	184.91	159.45	180.35
	Total	76	47.32	31.52	3.61	40.12	54.53	16.35	180.35

GRAPH.8 comparison of smokers and non-smoker subjects for microalbuminuria



84.09% of the smokers of the total smoking subjects had higher urine albumin and 15.90% of the total non-smoking subjects had higher urine albumin concentration.

GRAPH.9 comparison of mean urinary albumin creatinine ratio between smokers and non-smokers



95.45 % of smokers had higher urine albumin creatinine ratio (ACR) of the total smoking subjects and 4.54% of non-smokers had higher urine Albumin creatinine ratio.

DISCUSSION

This study was conducted in Government Rajaji Hospital, Madurai which is affiliated to Madurai Medical College, Madurai. 120 non diabetic, normotensive and non-obese subjects were taken from the general medicine op clinic of the govt. rajaji hospital. The total number of smokers with smoking being defined as those who have smoked >20 bidis for more than 5 years are 76. The rest of the 44 subjects were age matched and taken as the control population. The period of study was 4 months.

Age Distribution of the Study Subjects :

In our study the mean age of the study subjects is 47.27. The minimum age is 33 and the maximum age is 64. The mean age for smokers is 47.89 and the mean age for the non-smokers is 46.18. The p value is 0.169 on comparing the two means and hence the two groups are comparable with respect to age. In similar study conducted by R.K.Gupta et al in mahatma Gandhi medical college and hospital, Jaipur india with a total of 120 subject, the mean age of smokers is 48.68 and the mean age for non-smokers is 46.10 which is similar to our study. In the PREVEND study conducted in Netherlands the mean age for smokers is around 47. Our

study included individuals in the age group from 30 to 70 years. This was similar to the study conducted by R.K.Gupta et al.

Distribution of the baseline physical and biochemical characteristics:

Body mass index:

The mean body mass index for the smokers is 22.128 and for the non-smokers is 22.525. The minimum value is 18.9 and the maximum value is 24.7. The p value comparing the two means by independent T test is 0.060. so there was no statistically significant difference between the two means. In another study conducted by R.K.Gupta et al the mean BMI in smokers was 23.97 and for non-smokers was 24.52.

Blood pressure:

The mean value for systolic blood pressure among smokers is 124.16 mmhg and among non-smokers is 123.73 mmhg. The p value using the independent T test is 0.572. There was no statistically significant difference between the two means. The mean diastolic blood pressure among smokers is 75.50mmhg and the mean diastolic blood pressure among non-smokers is 75.61mmhg. The p value comparing the two means is 0.867 and so there is no statistically significant difference between the two means. In the study conducted by R.K.Gupta the mean systolic blood pressure among smokers was 124.40mmhg and among

non-smokers was 124.25mmhg. This is similar to our study. The diastolic blood pressure among smokers in that same study was 77.35 mmhg among smokers and 77.75 mmhg among non-smokers and this is close to our study. In the PREVEND study conducted in Netherlands the systolic blood pressure mean was around 75 mmhg in non-smokers and 73 mmhg in smokers. This was similar to our study.

Lipid profile:

The total cholesterol mean for smokers in our study is 151.62 mg/dl and the mean for non-smokers is 151.45 mg/dl. The p value comparing these two means is 0.846 and hence the difference is not statistically significant. The Low density lipoprotein (LDL) mean for smokers is 89.116 mg/dl and the mean for non-smokers is 84.977. The p value comparing the two means is 0.001. The normal range for LDL is between 70 and 100 mg/dl. and so this difference is not clinically significant. The mean value for triglyceride for smokers is 126.99 mg/dl and for non-smokers is 123.07 mg/dl. The p value comparing these two is 0.014. The mean value for very low density lipoprotein for smokers is 25.397 mg/dl and for non-smokers is 24.614 mg/dl. The p value comparing these two means is 0.014. Hence the differences were not statistically significant. In the study conducted by R.K.Gupta et al the mean value for smokers for LDL and TG were 88.48 mg/dl and 115.30 mg/dl respectively. The mean LDL for

non-smokers for LDL and TG were 85.05mg/dl and 119.14 mg/dl respectively. These values were similar to our study. The HDL mean for smokers is 37.05 mg/dl and the mean for non-smokers is 42 mg/dl. The p value comparing these two means is 0.001 which is statistically significant. This difference is important because the normal range for HDL is between 40 and 60 mg/dl. so the smokers in our study had significantly low HDL when compared to the non-smokers group. Low HDL in smokers has been reported in many studies. Similar results were obtained in the study conducted by R.K.GUPTA et al in which smokers had a mean HDL of 36.66 mg/dl. A study conducted by kavita S.gamit et al including 130 patients in which lipid profile among smokers were studied showed a similar result with a low HDL among the smoking population. Another study comparing 50 smokers and 50 healthy volunteers conducted by N.S. neki al also showed significant reduction in HDL levels among smokers.

Renal parameters:

The mean value for serum urea is 24.46 mg/dl for smokers and 25.39 mg/dl for non-smokers. The P value comparing the means is 0.294. Thus the difference is not statistically significant. The mean value for serum creatinine for smokers is 0.75 and the mean value for the non-smoking group is 0.74mg/dl. The p value is 0.701. Thus the difference is not

statistically significant. The creatinine clearance mean value for smokers is 102.310 ml/min/1.71m2 and for non-smokers is 105.355 ml/min/1.72m2. The p value comparing the means is 0.535. hence the difference is not statistically significant.

Hence the two groups were comparable in all parameters except for HDL levels.

Comparison of urine microalbumin between study and control:

In this study which contains 120 subjects. 76 were smokers and 44 were non-smokers. In this study the number of smoking subjects who had high urine albumin levels (>20mg/L) were 69(90.8%) and the number of non-smoking subjects who had high urine albumin levels were 7(15.9%). The microalbuminuria was directly related to the amount of smoking in pack years. The mean urine albumin for smokers is 47.3271 mg/L and the mean urine albumin for non-smokers is 18.9402 mg/L. The chi square P value comparing these two means is <0.001.Hence the difference is statistically significant and this shows that smokers had significantly high urine albumin levels when compared to non-smokers. The mean urinary albumin for smokers related to pack years is as follows,

1)5-9 pack years = 33.38mg/L

2)10-14 pack years = 48.84mg/L

3)15-19 pack years = 57.19 mg/L

4)>20 pack years = 171.15 mg/L

9.2% of smokers and 84.1 % of non-smokers had normal urine albumin levels. In the study conducted by R.K.gupta et al which included 120 subjects with 80 smokers and 40 non-smokers, 91.25%(73) of smokers and 22.5%(9) non-smokers had high urine albumin levels. In the PREVEND study conducted in Netherlands also showed that non-diabetic normotensive and non-obese smokers had a significantly higher urine albumin levels when compared to non-smokers. In another study conducted by Hitesh shah et al in Gujarat comparing 50 tobacco and 50 healthy volunteers the tobacco chewers had significantly high mean urine albumin of 373±13mg/L when compared to healthy volunteers. In a Japanese study that included 10,118 middle aged individuals with normal renal parameters and no proteinuria at entry showed that after a followup of six years smokers had a higher incidence of proteinuria and they were at a 1.51 time high risk of developing proteinuria than their non-smoking counterparts.

Comparison of Urine albumin creatinine ratio(ACR) between study and control group:

The number of smoking subjects who had high urine albumin creatinine ratio were 63(82.9%) and the number of non-smoking subjects who had high urine albumin creatinine ratio were 2(4.5%). 13(17.1%) of smokers and 42(95.5%) of non-smokers had urine albumin creatinine ratio within normal limits. The mean urinary albumin creatinine ratio for smokers is 74.0617 micro g/mg and the mean urinary albumin creatinine ratio for non-smokers is 20.6566 micro g/mg. The p value by chi square test comparing these two means is <0.001. Hence the difference is statistically significant and this shows that smokers have significantly high urinary albumin creatinine ratio when compared to non-smokers. The mean urinary albumin related to pcak years of smoking is as follows,

1) 5-9 pack years = 48.92 micro g/mg
2) 10-14 pack years = 68.74 micro g/mg
3) 15-19 pack years = 125.76 micro g/mg
4) >20 pack years = 221.77 micro g/mg.

This shows that the urinary albumin creatinine ratio is directly related to the number of pack years of smoking.

In the study conducted by R.K.gupta et al including 120 subjects(80 smokers and 40 non-smokers), 64(80%) smokers and 2

non-smokers(5%) had high urinary albumin creatinine ratio which is similar study.

A recent study has showed that subjects with both systemic hypertension and left ventricular hypertrophy smoking more than 20 cigarettes per day had a 1.6 fold higher prevalence of microalbuminuria and a 3.7 fold higher prevalence of macroalbuminuria. Several similar studies have documented that smoking is an independent risk factor for micro/macro albuminuria and progression to end stage kidney disease.

One of the mechanisms by which smoking causes albuminuria is by the formation of advanced glycation end products (AGEPs). When reducing sugars react with the amino groups of lipids, nucleic acids and plasma proteins, the advanced glycation end products are formed. The compounds increase the vascular permeability and are also responsible for the progression of vasculopathy and nephropathy in end stage diabetic kidney disease. Glycotoxins present in the smoke react with plasma and tissue proteins and lead to AGEP formation which has the same effect on renal and systemic vessels. One another mechanism by which smoking affects the kidney is by insulin resistance. Studies have shown that smoking can induce insulin resistance in non-diabetic subjects. Insulin resistance has been linked with albuminuria and renal function detoriation. Both these machansims act through inducing endothelial

damage thus bringing about an imbalance between contracting and relaxing substances in the endothelium. Studies have shown that smokers have high endothelin concentration and low concentration of vasodilatory substances.

In our study non-diabetic, normotensive and non-obese smokers had a higher mean urinary albumin concentration when compared to non-smokers and the mean urinary albumin in smokers were directly related to the pack years of smoking. Smokers also had a high urinary albumin creatinine ratio when compared to non-smokers when compared to non-smokers and the urine ACR was directly related to the pack years of smoking. In our study all the baseline biochemical parameters were comparable except the HDL levels which were significantly low when compared to non-smokers.

The limitations in our study were a small number of subjects, single centre data and screening with one timed urine samples.

CONCLUSION

- Normotensive and non-diabetic smokers have significantly higher levels of urine albumin when compared to non-smokers.
- Normotensive and non-diabetic smokers have significantly higher levels of urine albumin creatinine ratio (ACR) when compared to non-smokers.
- The high urine albumin levels and high urine albumin creatinine ratio (ACR) levels are directly related to the quantity of smoking expressed in pack years.
- The proportion of smokers having high urine albumin levels is 6 fold times the non-smokers and the proportion of smokers having high urine albumin creatinine ratio (ACR) is 18 fold times the non-smokers.
- Smokers had significantly low HDL levels when compared to non-smokers.

SUMMARY

Smoking has major adverse effects on health and it predisposes to ischemic heart disease, chronic bronchitis, emphysema, stroke and tumors of lung, gastrointestinal system, urinary tract , etc. smoking reduces renal blood flow and long term smoking increases the risk of progression to end stage renal disease. Smoking causes a transient rise in systolic blood pressure, reduces glomerular filtration rate and renal plasma flow. It increases the risk of renal function deterioration in elderly. Various studies has shown that smoking causes a dose dependent increase in urine albumin excretion. It increases the risk of albuminuria and renal function deterioration in the general population. Stopping the habit of smoking reverses these adverse effects to a significant extent in the long term. In a study on lean subjects with essential hypertension it was found that the microalbuminuria prevalence in smokers was twice the amount found in non-smokers. In smokers with diabetes mellitus the microalbuminuria prevalence is increased, the time period between the onset of albuminuria and diabetes mellitus is shortened, the risk of progression from microalbuminuria to

macroalbuminuria is increased, the risk of progression to end stage renal disease is increased and the risk of ischemic nephropathy is increased.

In non-diabetic renal disease such a lupus nephritis and IgA nephropathy the risk of progression to end stage renal disease in increased in smokers. smoking is also reported to increase the risk of cholesterol microembolism and thus increases the of progression of ischemic nephropathy. Smoking also reduces the allograft survival in renal transplant recipients. Multiple studies have shown that microalbuminuria is an independent risk factor for cardiovascular disease and renal disease. It a marker of endothelial dysfunction and it predicts the future risk of progression to end stage renal failure, progression to overt proteinuria and increase in serum creatinine. The heart outcome and prevention study (HOPE) study has shown that smoking was an independent predictor of microalbuminuria in both diabetic and non-diabetic population. The prevention of renal and vascular end stage disease or PREVEND study showed that smokers had a high statistically significant urine albumin excretion when compared to nonsmokers.

In our study which included 120 subjects from govt.rajaji hospital, 76 were smokers and 44 were non-smokers. microalbuminuria was

defined as urine albumin excretion above 20mg/L and urine albumin creatinine ratio was defined as a value above 30 micro g/mg. 69 smokers(90.8%) of smokers and 7non-smokers (15.9%) had microalbuminuria. 63 smokers(82.9%) of smokers and 2 non smokers (4.5%) had high urine albumin creatinine ratio(ACR). The mean urine albumin in smokers was 47.3271 mg/L and the mean urine albumin in non-smokers is 18.9402 mg/L. The P value using chi square test is <0.001. The mean urinary albumin creatinine ratio is 74.0617 and for non-smokers is 20.6566. The p value using the chi square test is <0.001. Hence this shows that the number of smokers having microalbuminuria and the high urinary albumin creatinine ratio is significantly high than the non-smoking subjects. Our study also shows that the microalbuminuria and high urine albumin creatinine ratio are directly proportional to the number of pack years of smoking, Which means that urine albumin excretion and albumin creatinine ratio increase with the duration of smoking. Our study has also shown that smokers had statistically significant low HDL when compared to non-smokers. This topic needs further attention and further research is needed on the high prevalence of smoking addiction in the indian community and its impact on the renal function and cardiovascular risk.

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PROFORMA

Name: **Age/Sex:** **Occupation:**

OP.No

Address:

Past history:

DM, HTN, CAD, CVA, CKD, Hypothyroidism, Nephrotic syndrome,

Drug history: H/o any drug intake(anti hypertensives, OHAs, cardiovascular drugs)

Family history: CAD, Obesity, renal disorders

Personal history:- H/o substance abuse

Smoking in pack years:

Clinical examination:

General examination:

Pallor, Clubbing, Icterus, corneal arcus , xanthoma Lymphadenopathy, Cyanosis , Pedal oedema

Ht (in meter): weight (in kg) : BMI:

Fundus examination: Right eye : Left eye:

Vitals:

Pulse: BP:

RR: Temperature:

Systemic examination:

CVS :

RS :

ABDOMEN :

CNS

Laboratory investigations:

1)Fasting blood sugar (Venous blood sample for glucose analysis)

2)Total cholesterol

3)High density cholesterol

4)Low density cholesterol

5)very low density cholesterol

6)Triglycerides

7)Blood urea

8)Serum creatinine

9)Urine albumin and albumin-creatinine ratio

ABBREVIATIONS

HDL - High Density Lipoprotein

LDL - Low Density Lipoprotein

VLDL - Very Low Density Lipoprotein

TG - Triglycerides

TC - Total cholesterol

PGF2 - 8-iso-prostaglandin F2

TBARS- Thiobarbituric acid reactive substances

GSH - Glutathione

PMN - Poly morphonuclear neutrophil.

CRP - C-reactive protein

TNF - Tumour necrosis factor

t-PA - tissue plasminogen activator

PAI-I - Plasminogen activator inhibitor

PAH - Poly aromatic hydrocarbons

NNN - N-nitrosonornicotine

NNK - N-nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

DNA - Deoxy ribo nucleic acid.

LIFE - Losartan intervention for endpoint reduction in Hypertension.

AER - Albumin excretion rate.

GFR - Glomerular filtration rate.

ACTH - Adrenocorticotropic hormone

IDNT - Irbesartan diabetic nephropathy trial.

ANCA - Anti-neutrophil cytoplasmic antibody.

PREVEND - Prevention of renal and vascular endstage disease intervention.

cGMP - cyclic guanosine monophosphate.

MASTER CHART-SMOKERS

S.NO	NAME	SEX	AGE (yrs)	HEIGHT(meter)	WEIGHT (KG)	BMI	SBP(mm hg)	DBP(mm hg)	FBS(mg/dl)	TC(mg/dl)	LDL(mg/dl)	HDL(mg/dl)	TG(mg/dl)	VLDL(mg/dl)
1	KRISHNAN	M	42	1.65	62	22.77	124	70	80	148	89.2	36	114	22.8
2	KARUPPAIYAH	M	45	1.64	61	22.68	122	72	76	156	92.4	38	128	25.6
3	SITARAM	M	44	1.66	63	22.86	124	74	78	160	79.2	56	124	24.8
4	MUNIYAPPAN	M	51	1.65	63	23.14	128	78	82	147	86	37	120	24
5	CHINNAYAH	M	45	1.63	62	23.34	120	76	90	148	82.4	42	118	23.6
6	RAMAR	M	50	1.6	59	23.05	128	74	92	150	79.6	46	122	24.4
7	SELVAM	M	48	1.64	60	22.31	128	78	95	152	88.4	39	123	24.6
8	RAMACHAND	M	54	1.64	58	21.56	126	80	90	155	96	34	125	25
9	ALI MUHAMMED	M	44	1.65	59	21.67	128	78	76	156	98.6	33	122	24.4
10	KALLIAPPAN	M	53	1.64	60	22.31	122	70	78	156	92.8	40	116	23.2
11	RAMAN	M	46	1.68	58	20.55	124	72	80	150	88.4	38	118	23.6
12	MALAISAMY	M	56	1.67	60	21.51	130	74	82	147	86.6	35	127	25.4
13	DURAI RAJ	M	46	1.65	58	21.30	128	76	85	146	84	38	120	24
14	SIVA PRAKASH	M	52	1.66	60	21.77	126	78	87	158	98.4	36	118	23.6
15	KUMARESAN	M	42	1.62	62	23.62	128	70	76	150	89.8	37	116	23.2
16	MUTHU	M	55	1.65	60	22.04	126	72	78	148	87	38	115	23
17	PALANI	M	40	1.62	55	20.96	122	76	88	146	80.4	43	113	22.6
18	GANESAN	M	53	1.65	60	22.04	132	74	76	144	86.2	35	114	22.8
19	KULANTHAI	M	37	1.62	58	22.10	118	78	86	148	85.6	39	117	23.4
20	CHELLAIYAH	M	52	1.62	57	21.72	126	76	74	150	91.4	34	123	24.6
21	MEGAVARNAN	M	38	1.59	55	21.76	116	74	83	152	95	33	120	24
22	BHAGADUR	M	53	1.64	60	22.31	114	78	90	154	91	37	130	26
23	RAJA	M	54	1.65	57	20.94	118	80	91	153	90.8	36	131	26.2
24	PAULSAMY	M	39	1.66	66	23.95	120	80	88	154	88	42	120	24
25	MUTHUSAMY	M	63	1.68	64	22.68	130	82	76	156	92	38	130	26
26	DURAI RAJ	M	41	1.63	65	24.46	126	80	79	148	88.4	36	118	23.6
27	ALAGARSAMY	M	51	1.64	62	23.05	120	78	85	147	89	34	120	24
28	RAMAR	M	47	1.67	60	21.51	128	78	97	148	88.2	35	124	24.8
29	RAJA	M	51	1.62	57	21.72	122	70	83	149	89.4	36	118	23.6
30	MURUGAN	M	46	1.64	56	20.82	120	74	95	147	86.8	37	116	23.2
31	RAJAGOPAL	M	53	1.65	55	20.20	120	76	76	148	91	34	115	23
32	ALLABAKS	M	40	1.63	51	19.20	120	74	73	148	88	36	120	24
33	SONAI	M	52	1.66	52	18.87	122	76	86	146	86.8	34	126	25.2
34	VELU	M	45	1.69	57	19.96	124	76	89	148	87.2	38	114	22.8

35	PRABHAKARAN	M	48	1.65	62	22.77	126	78	86	146	82.4	39	123	24.6
36	LAKSHMANAN	M	40	1.63	54	20.32	128	80	85	148	82.2	40	129	25.8
37	PERIYASAMY	M	50	1.64	60	22.31	126	80	89	150	86.8	40	116	23.2
38	KUMAR	M	34	1.63	60	22.58	120	70	90	151	89.4	36	128	25.6
39	MARIMUTHU	M	59	1.68	57	20.20	118	72	95	153	90.2	38	124	24.8
40	PITCHAIRAJAN	M	33	1.63	58	21.83	126	76	97	154	94	34	130	26
41	CHELLADURAI	M	57	1.69	59	20.66	120	70	89	149	92.2	33	119	23.8
42	RAJA	M	37	1.65	59	21.67	126	72	90	150	87.2	36	134	26.8
43	RAMAN	M	56	1.63	55	20.70	116	70	94	153	94.4	35	118	23.6
44	SELVAM	M	45	1.66	60	21.77	116	70	97	160	98	38	120	24
45	AASAI	M	60	1.62	59	22.48	120	72	76	158	97.4	36	123	24.6
46	MAYANDI	M	47	1.65	59	21.67	128	74	78	154	86	43	125	25
47	MANOKARAN	M	54	1.62	56	21.34	124	74	83	160	99.4	35	128	25.6
48	SANTHAKUMAR	M	42	1.62	60	22.86	126	76	85	156	92	37	135	27
49	CHELLAM	M	58	1.65	62	22.77	124	78	89	154	95.4	35	118	23.6
50	BALAMURUGAN	M	44	1.65	61	22.41	120	70	80	148	79.6	45	117	23.4
51	MUNIYANDI	M	52	1.64	62	23.05	118	70	76	147	87.8	32	136	27.2
52	RAJAGOPAL	M	44	1.65	60	22.04	128	76	89	148	90.6	30	137	27.4
53	GURUSAMY	M	51	1.67	59	21.16	124	76	83	149	79.2	42	139	27.8
54	SUNDAR	M	45	1.65	56	20.57	126	76	87	147	80	39	140	28
55	MANOKARAN	M	64	1.61	58	22.38	120	70	82	148	88.2	34	129	25.8
56	MOORHTY	M	40	1.62	59	22.48	128	80	80	147	82.6	36	142	28.4
57	KARUPUSAMY	M	60	1.64	60	22.31	124	70	87	148	85.6	35	137	27.4
58	PANDI	M	44	1.63	62	23.34	126	76	83	149	83.4	38	138	27.6
59	SUBRAMANI	M	59	1.65	62	22.77	128	80	87	155	90	37	140	28
60	LASHMANAN	M	45	1.65	62	22.77	128	76	89	156	94.4	33	143	28.6
61	ALGARSAMY	M	55	1.65	65	23.88	126	80	90	153	90.8	35	136	27.2
62	MUNIYASAMY	M	40	1.65	62	22.77	120	72	92	149	86.2	37	129	25.8
63	MURUGESH	M	56	1.64	62	23.05	128	76	95	160	98.2	38	119	23.8
64	PRAKASH	M	47	1.63	60	22.58	122	74	97	161	98	35	140	28
65	KATHIR	M	55	1.65	62	22.77	120	72	80	161	93	39	145	29
66	RATHINAM	M	45	1.66	63	22.86	124	76	76	158	94	34	150	30
67	RAJA	M	46	1.64	62	23.05	128	76	84	150	84.2	36	149	29.8
68	DEVARAJ	M	48	1.64	60	22.31	126	74	89	152	86.4	37	143	28.6
69	MANI	M	45	1.65	64	23.51	126	78	83	148	80.4	38	148	29.6
70	RAJ KUMAR	M	48	1.63	60	22.58	128	80	98	146	84	35	135	27
71	AHMED	M	46	1.63	60	22.58	128	78	82	149	89	34	130	26
72	YUSUF	M	44	1.65	64	23.51	130	82	81	160	96.6	37	132	26.4
73	MANI	M	42	1.62	61	23.24	128	80	89	158	95	36	135	27
74	DHANRAJ	M	42	1.65	60	22.04	128	82	84	159	93	38	140	28
75	AJITH	M	40	1.65	62	22.77	124	76	78	148	84.6	36	137	27.4
76	KUMAR	M	45	1.67	62	22.23	126	78	72	156	97	35	120	24

S.NO	NAME	SEX	AGE (yrs)	SERUM UREA (mg/dl)	SERUM CREATININE (mg/dl)	CREATININE CLEARANCE (ml/min/1.73m2 `	URINE MICROALBUMIN (mg/L)	URINE ACR (micro g/mg)	PACK YEARS
1	KRISHNAN	M	42	33	0.8	105.49	32.02	56.49	7
2	KARUPPAIYAH	M	45	22	0.8	100.61	35.03	57.83	7
3	SITARAM	M	44	34	0.8	105.00	35.78	60.56	6
4	MUNIYAPPAN	M	51	25	0.8	97.34	31.56	58.58	7
5	CHINNAYAH	M	45	26	0.9	90.90	37.12	59.21	5
6	RAMAR	M	50	17	0.7	105.36	50.21	66.45	12
7	SELVAM	M	48	18	0.7	109.52	51.34	68.67	11
8	RAMACHANDRAN	M	54	20	0.7	98.97	57.45	180.81	17
9	ALI MUHAMMED	M	44	22	0.7	112.38	18.25	20.45	8
10	KALLIAPPAN	M	53	19	0.7	103.57	50.45	57.45	14
11	RAMAN	M	46	18	0.7	108.17	34.78	60.13	8
12	MALAISAMY	M	56	24	0.7	100.00	56.25	100.56	15
13	DURAI RAJ	M	46	34	0.8	94.65	37.89	61.23	7
14	SIVA PRAKASH	M	52	26	0.7	104.76	32.67	60.99	9
15	KUMARESAN	M	42	22	0.8	105.49	33.99	59.54	6
16	MUTHU	M	55	20	0.7	101.19	53.24	70.76	14
17	PALANI	M	40	28	0.8	95.49	18.26	22.56	8
18	GANESAN	M	53	20	0.7	103.57	51.34	80.56	14
19	KULANTHAIVEL	M	37	18	0.7	118.53	35.89	59.76	7
20	CHELLAIYAH	M	52	30	0.8	87.08	34.67	59.86	9
21	MEGAVARNAN	M	38	32	0.8	97.40	17.25	19.34	7
22	BHAGADUR	M	53	30	0.7	103.57	52.31	74.35	13
23	RAJA	M	54	28	0.7	97.26	55.76	99.56	19
24	PAULSAMY	M	39	24	0.9	102.87	37.45	58.58	8
25	MUTHUSAMY	M	63	26	0.7	97.78	180.35	190.56	25
26	DURAI RAJ	M	41	30	0.8	111.72	36.99	26.45	9
27	ALAGARSAMY	M	51	32	0.8	95.80	35.46	60.98	8
28	RAMAR	M	47	28	0.7	110.71	31.45	61.25	7
29	RAJA	M	51	27	0.7	100.65	32.17	57.65	9
30	MURUGAN	M	46	26	0.7	104.44	37.42	59.74	7
31	RAJAGOPAL	M	53	23	0.7	94.94	58.75	186.78	17
32	ALLABAKS	M	40	20	0.7	101.19	16.35	18.45	8
33	SONAI	M	52	26	0.6	105.93	36.77	58.54	9
34	VELU	M	45	30	0.7	107.44	35.49	56.49	7
35	PRABHAKARAN	M	48	20	0.8	99.03	53.56	82.53	13
36	LAKSHMANAN	M	40	18	0.8	93.75	38.49	19.45	7
37	PERIYASAMY	M	50	17	0.7	107.14	50.78	83.64	14

38	KUMAR	M	34	19	0.8	110.42	38.45	18.65	6
39	MARIMUTHU	M	59	30	0.7	91.61	159.45	220.45	25
40	PITCHAIRAJAN	M	33	23	0.8	107.74	18.45	20.45	7
41	CHELLADURAI	M	57	22	0.6	113.36	58.11	175.45	18
42	RAJA	M	37	20	0.7	120.58	39.12	57.74	7
43	RAMAN	M	56	19	0.7	91.67	55.67	167.65	18
44	SELVAM	M	45	26	0.7	113.10	37.13	59.83	6
45	AASAI	M	60	25	0.6	109.26	59.01	156.56	18
46	MAYANDI	M	47	28	0.8	95.26	36.65	61.45	8
47	MANOKARAN	M	54	29	0.7	95.56	51.21	75.68	14
48	SANTHAKUMAR	M	42	30	0.7	116.67	36.87	60.54	8
49	CHELLAM	M	58	32	0.7	100.87	57.12	98.45	17
50	BALAMURUGAN	M	44	25	0.9	90.37	36.74	57.98	9
51	MUNIYANDI	M	52	28	0.7	108.25	49.56	80.41	13
52	RAJAGOPAL	M	44	24	0.8	100.00	36.73	19.1	7
53	GURUSAMY	M	51	31	0.7	104.19	47.67	54.76	13
54	SUNDAR	M	45	26	0.8	92.36	37.64	61.66	7
55	MANOKARAN	M	64	28	0.8	76.53	172.45	245.56	26
56	MOORHTY	M	40	23	0.8	102.43	17.45	23.67	13
57	KARUPUSAMY	M	60	20	0.7	95.24	172.34	230.54	24
58	PANDI	M	44	26	0.8	103.33	35.23	60.43	7
59	SUBRAMANI	M	59	23	0.8	87.19	57.21	96.56	19
60	LASHMANAN	M	45	25	0.8	102.26	32.99	56.78	8
61	ALGARSAMY	M	55	23	0.7	109.62	57.46	94.57	18
62	MUNIYASAMY	M	40	17	0.7	123.02	37.56	23.6	7
63	MURUGESH	M	56	20	0.7	103.33	57.56	69.73	17
64	PRAKASH	M	47	18	0.8	96.88	48.86	68.34	13
65	KATHIR	M	55	23	0.8	91.49	55.98	82.51	18
66	RATHINAM	M	45	27	0.8	103.91	37.65	54.78	8
67	RAJA	M	46	20	0.8	101.18	33.29	59.11	8
68	DEVARAJ	M	48	21	0.7	109.52	48.97	73.45	14
69	MANI	M	45	22	0.7	120.63	34.44	58.74	9
70	RAJ KUMAR	M	48	28	0.8	95.83	49.67	70.42	13
71	AHMED	M	46	31	0.9	87.04	37.11	58.54	7
72	YUSUF	M	44	25	0.9	94.81	36.65	59.87	8
73	MANI	M	42	22	0.8	103.78	35.23	20.16	7
74	DHANRAJ	M	42	20	0.7	116.67	36.75	60.54	8
75	AJITH	M	40	18	0.8	107.64	16.67	17.65	7
76	KUMAR	M	45	29	0.8	102.26	34.77	59.54	8

MASTER CHART FOR NON-SMOKERS

S.NO	NAME	SEX	AGE (yrs)	HEIGHT(meter)	WEIGHT(KG)	BMI	SBP(mm hg)	DBP(mm hg)	FBS(mg/dl)	TC (mg/dl)	LDL(mg/dl)	HDL(mg/dl)	TG(mg/dl)	VLDL(mg/dl)
1	MANI	M	41	1.64	64	23.80	126	70	78	149	84	42	115	23
2	MURUGAN	M	44	1.63	64	24.09	124	71	76	155	85	41	129	25.8
3	THAYUMANAVAN	M	44	1.65	65	23.88	126	74	78	160	85	42	126	25.2
4	MOHAN	M	50	1.67	63	22.59	126	76	80	148	85	43	122	24.4
5	MUTHUVEL	M	45	1.65	67	24.61	118	76	88	149	85	45	119	23.8
6	RAMESH	M	48	1.6	59	23.05	130	80	90	151	85	42	123	24.6
7	KULANTHAIVEL	M	48	1.61	59	22.76	126	78	90	153	85	40	124	24.8
8	MARUDHAN	M	52	1.6	59	23.05	128	80	90	156	85	42	126	25.2
9	ABDUL	M	46	1.59	55	21.76	126	78	74	159	85	40	123	24.6
10	BALA	M	52	1.62	61	23.24	120	72	76	157	85	40	120	24
11	MURUGUAN	M	45	1.67	54	19.36	126	72	78	149	85	45	120	24
12	JAFFER	M	45	1.66	63	22.86	132	80	80	148	85	42	128	25.6
13	RAMESH	M	45	1.7	58	20.07	126	80	84	147	85	41	121	24.2
14	MUTHUVEL	M	40	1.71	60	20.52	128	78	86	159	85	40	119	23.8
15	PALANIVEL	M	41	1.57	61	24.75	126	70	75	151	85	43	118	23.6
16	VELU	M	54	1.58	60	24.03	128	72	75	149	85	42	120	24
17	PARAMSIVAM	M	41	1.6	55	21.48	124	80	85	147	85	41	114	22.8
18	CHINNARAJ	M	52	1.64	60	22.31	130	74	75	145	85	42	118	23.6
19	ILUMALAIYAN	M	38	1.62	59	22.48	120	76	84	149	85	43	118	23.6
20	AJITH KUMAR	M	51	1.62	59	22.48	124	76	73	151	85	42	124	24.8
21	DHANAM	M	39	1.59	57	22.55	118	74	82	153	85	41	121	24.2
22	MANI	M	44	1.62	58	22.10	116	72	88	155	85	42	131	26.2
23	KARTHIK	M	53	1.65	58	21.30	120	80	90	154	85	43	132	26.4
24	CHELLADURAI	M	39	1.65	65	23.88	122	80	87	156	85	42	121	24.2
25	SHANMUGAM	M	62	1.65	64	23.51	132	80	75	157	85	40	131	26.2
26	VELAYUDHAM	M	41	1.62	64	24.39	128	80	75	149	85	40	126	25.2
27	MARIYAPPAN	M	50	1.63	62	23.34	122	78	84	147	85	42	121	24.2
28	PALANIYAPPAN	M	46	1.66	60	21.77	126	80	95	149	85	42	126	25.2
29	MICHAEL RAJ	M	50	1.61	58	22.38	120	70	82	150	85	43	119	23.8
30	KALAIRAJAN	M	45	1.63	56	21.08	118	74	94	148	85	42	122	24.4
31	KURUVAN	M	51	1.64	60	22.31	122	76	75	149	85	41	122	24.4
32	STEPHEN DHANPAL	M	40	1.62	57	21.72	118	74	72	149	85	41	121	24.2
33	BALAMURUGAN	M	51	1.65	58	21.30	120	76	85	147	85	41	125	25
34	VADAMALAI	M	44	1.68	60	21.26	124	76	86	149	85	41	118	23.6
35	KANNAN	M	46	1.69	62	21.71	126	80	85	147	85	42	121	24.2
36	MALAISAMY	M	41	1.59	58	22.94	126	80	84	149	85	43	130	26

37	BALU	M	48	1.63	60	22.58	124	78	88	151	85	45	118	23.6
38	NAGARATHINAM	M	36	1.62	60	22.86	122	70	88	150	85	42	126	25.2
39	SELVARAJ	M	57	1.67	63	22.59	120	72	90	154	85	45	124	24.8
40	SELVAM	M	36	1.62	60	22.86	124	80	96	155	85	44	132	26.4
41	ABDULLAH	M	54	1.68	64	22.68	120	70	88	150	85	43	124	24.8
42	KANNAN	M	38	1.64	60	22.31	124	72	85	151	85	42	136	27.2
43	LOGU	M	55	1.62	59	22.48	120	72	93	152	85	42	120	24
44	JUSTIN SAGAYARAJ	M	44	1.65	60	22.04	118	70	94	161	85	41	121	24.2

S.NO	NAME	SEX	AGE(yrs)	SERUM UREA (mg/dl)	SERUM CREATININE (mg/dl)	CREATININE CLEARANCE (ml/min/1.73m)	URINE MICROALBUMIN (mg/L)	URINE ACR (micro g/mg)
1	MANI	M	41	33	0.8	110.00	17.21	18.99
2	MURUGAN	M	44	23	0.8	106.67	16.02	19.25
3	THAYUMANAVAN	M	44	34	0.8	108.33	17.03	20.65
4	MOHAN	M	50	26	0.8	98.44	16.04	16.75
5	MUTHUVEL	M	45	27	0.8	110.50	17	22.36
6	RAMESH	M	48	18	0.8	94.24	15.01	24.52
7	KULANTHAIVEL	M	48	18	0.7	107.70	16.02	19.04
8	MARUDHAN	M	52	24	0.7	103.02	32.67	17.89
9	ABDUL	M	46	24	0.7	102.58	15.04	21.76
10	BALA	M	52	20	0.8	93.19	31.23	23.76
11	MURUGUAN	M	45	20	0.7	101.79	15.33	24.98
12	JAFFER	M	45	24	0.8	103.91	16.05	20.03
13	RAMESH	M	45	34	0.8	95.66	17.11	22.85
14	MUTHUVEL	M	40	28	0.7	119.05	18	19.54
15	PALANIVEL	M	41	24	0.7	119.82	17.34	18.54
16	VELU	M	54	22	0.7	102.38	15.99	19.54
17	PARAMSIVAM	M	41	28	0.8	94.53	18.1	19.34
18	CHINNARAJ	M	52	22	0.7	104.76	35.54	20.42
19	ILUMALAIYAN	M	38	20	0.7	119.40	16.02	21.43
20	AJITH KUMAR	M	51	30	0.8	91.16	17.9	18.53
21	DHANAM	M	39	32	0.8	99.95	13.56	16.83
22	MANI	M	44	32	0.7	110.48	17.01	17.65
23	KARTHIK	M	53	28	0.7	100.12	15.23	20.65
24	CHELLADURAI	M	39	26	0.8	113.98	15.64	21.67
25	SHANMUGAM	M	62	28	0.7	99.05	45.11	40.54
26	VELAYUDHAM	M	41	30	0.8	110.00	16.04	18.65
27	MARIYAPPAN	M	50	32	0.8	96.88	15.01	19.65
28	PALANIYAPPAN	M	46	28	0.8	97.92	17.49	16.56
29	MICHAEL RAJ	M	50	27	0.7	103.57	12.45	15.65
30	KALAIRAJAN	M	45	28	0.7	105.56	31.07	18.45
31	KURUVAN	M	51	24	0.7	105.95	16	17.65
32	STEPHEN DHANPAL	M	40	22	0.7	113.10	16.34	18.45
33	BALAMURUGAN	M	51	28	0.7	102.42	17.11	17.57
34	VADAMALAI	M	44	30	0.7	114.29	15.02	20.04
35	KANNAN	M	46	22	0.8	101.18	14.34	18.76
36	MALAISAMY	M	41	19	0.8	99.69	16.34	20.45
37	BALU	M	48	18	0.7	109.52	29.01	18.65
38	NAGARATHINAM	M	36	20	0.8	108.33	15.02	18.46

39	SELVARAJ	M	57	30	0.7	103.75	34.1	36.21
40	SELVAM	M	36	23	0.8	108.33	15.01	21.75
41	ABDULLAH	M	54	23	0.7	109.21	16.55	22.87
42	KANNAN	M	38	22	0.7	121.43	17.1	19.56
43	LOGU	M	55	20	0.7	99.50	16.1	18.46
44	JUSTIN SAGAYARAJ	M	44	26	0.7	114.29	16.07	23.54

ETHICAL COMMITTEE APPROVAL

Ref.No.5053/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 06 .2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for June 2014 –
Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 24th June 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following project was approved by the committee

Dr.P.Rudreshwar rudreshwaripad@gmail.com	PG in MD (General Medicine), Madurai Medical college & Rajaji Hospital, Madurai.	A study on the incidence of microalbuminuria in non-diabetic normotensive smokers"	Approved.

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the E thical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

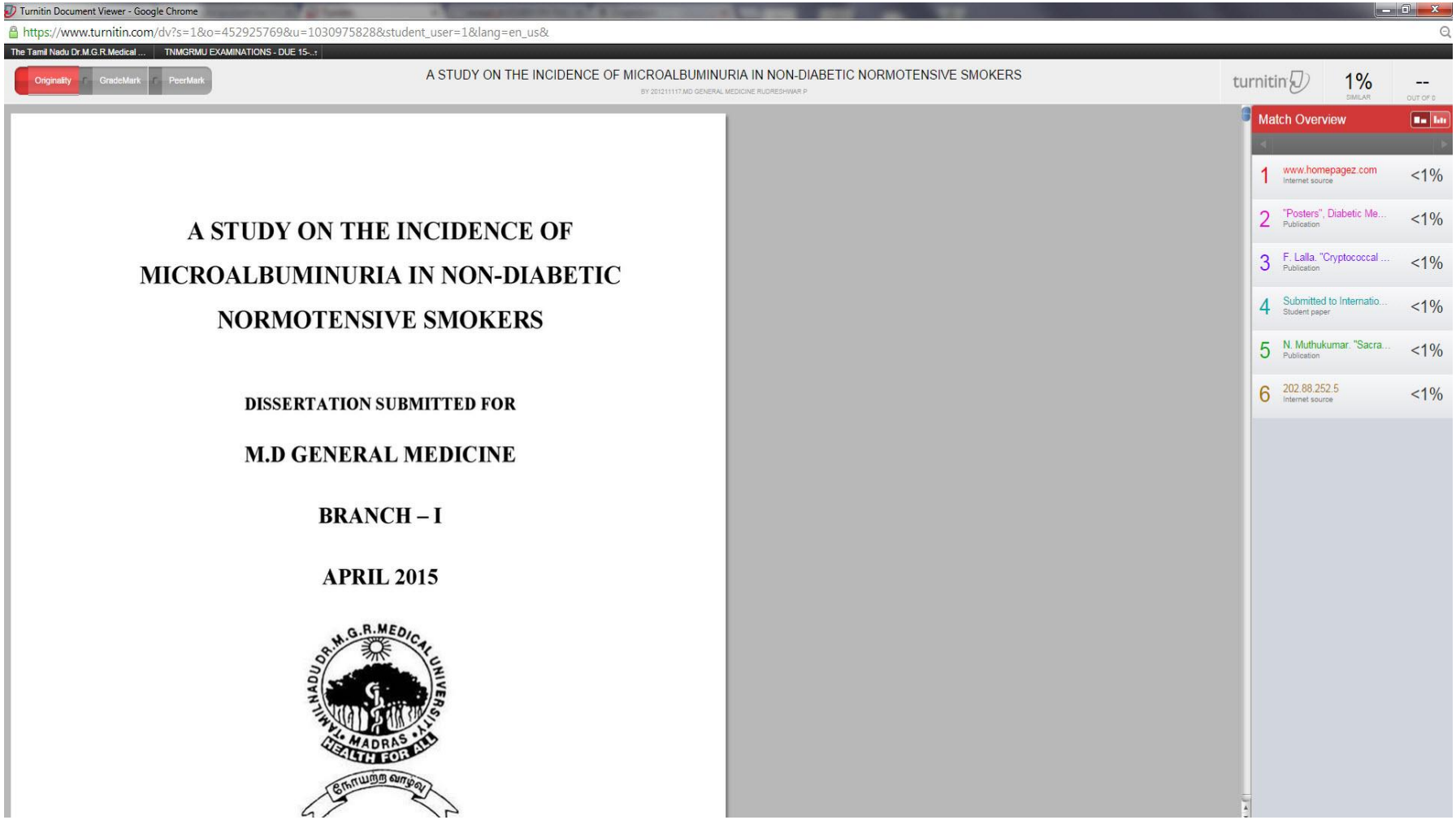
Member Secretary
Ethical Committee

Chairman
Ethical committee

31.7.14

DEAN/Convenor
Madurai Medical College & Govt.
Rajaji Hospital, Madurai- 20.

To
The above Applicant
-thro. Head of the Department concerned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BRANCH – I
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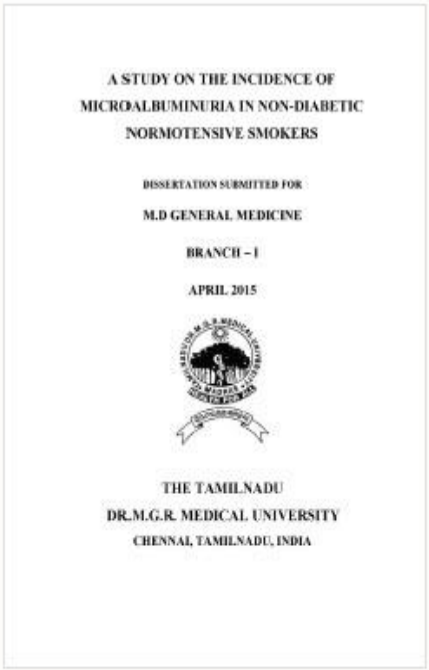

A STUDY ON THE INCIDENCE OF
MICROALBUMINURIA IN NON-DIABETIC
NORMOTENSIVE SMOKERS

DISSERTATION SUBMITTED FOR
M.D GENERAL MEDICINE
BRANCH – I
APRIL 2015

THE TAMILNADU
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